

Risk Factors for Urinary Tract Infections in Postmenopausal Women

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Background: Urinary tract infections (UTI) occur frequently in postmenopausal women and account for substantial morbidity and economic costs. Although extensively studied in younger women and older, debilitated women, the risk factors for UTI among healthy community-dwelling postmenopausal women have not been well described.

Methods: We conducted a population-based, case-control study of women aged between 55 and 75 years enrolled in a large, staff-model health maintenance organization. Cases were identified using computerized laboratory and outpatient records. Controls were randomly selected from the plan's enrollment files. We interviewed subjects regarding their habits, general health, and potential risk factors for UTI.

Results: We interviewed 899 study subjects and 911 controls. Sociodemographic characteristics were similar in subjects and controls. Most women were insured and white. Like younger women, postmenopausal women with

current UTI were more likely to be sexually active (odds ratio [OR], 1.42; 95% confidence interval [CI], 1.07-1.87) and have a history of UTI (OR, 4.20; 95% CI, 3.25-5.42). Like older debilitated women, study subjects were more likely to have diabetes mellitus (OR, 2.78; 95% CI, 1.78-4.35) and to be incontinent (OR, 1.36; 95% CI, 1.03-1.78). Oral estrogen replacement did not reduce UTI risk.

Conclusions: In this population, the risk factors of healthy community-dwelling postmenopausal women reflect the health status of women as they transition toward old age. Sexual activity, history of UTI, treated diabetes, and incontinence were all associated with a higher risk of UTI. The therapeutic role of oral estrogen remains uncertain. Prospective studies in different patient populations are needed to better understand the risk factors of UTI.

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MORE THAN 8 MILLION women in the United States seek medical attention for urinary tract infections (UTI) each year.¹ The annual incidence among women older than 50 years is 9% and these infections account for substantial morbidity.^{2,3} Risk factors for UTI have been well characterized among young healthy women and among older, debilitated women living in institutional settings.^{4,6} However, the risk factors for healthy community-dwelling postmenopausal women have not been well described.⁷

The major characteristics predisposing young women to UTI are sexual activity, use of spermicidal agents and contraceptive diaphragm, and a prior history of UTI.^{4,5} The major characteristics predisposing older, institutionalized women to UTI are advancing age, urologic abnormalities, and debilitating comorbid conditions.^{4,6}

The role of estrogen replacement therapy remains controversial. After menopause, the changes in the urinary tract due to lower levels of estrogen are believed to contribute to recurrent UTI.^{8,9} Two controlled trials of intravaginal estrogen creams found a significant risk reduction in recurrent UTI in women who use them.^{10,11} However, the effect of oral estrogen is less clear.¹²⁻¹⁴ Randomized trials and observational studies of oral estrogen have yielded conflicting results.^{2,7,12,15}

To date, research has focused on UTI in young healthy women and older, debilitated women, with relatively little attention to the 56 million generally healthy postmenopausal women aged between 55 and 75 years and residing in the community.⁷ For this reason, we performed a case-control study of acute, symptomatic UTI among generally healthy women in this age group to evaluate potential risk factors including sexual activity, history of UTI, dia-

betes mellitus, incontinence, and estrogen supplementation.

METHODS

We studied women at Group Health Cooperative of Puget Sound (GHC), a staff-model health maintenance organization with approximately 450 000 members in western Washington State at the time of this investigation. To aid in obtaining medical records and reduce the number of potential subjects, we limited eligibility to women receiving care in Pierce, King, and Snohomish counties of the state of Washington from 1994 through 1996.

Study subjects were women between the ages of 55 and 75 years with a recent diagnosis of acute UTI. Each month we reviewed the computerized laboratory files to identify all women whose urine culture during the preceding month grew 10^5 colonies or more of a uropathogenic organism per milliliter of urine. Since this process identified many more individuals than we could enroll, we selected only as many women as we expected to be able to interview within 4 weeks. They were selected consecutively in reverse chronological order based on the date of their UTI diagnosis. This minimized the interval between the UTI and the study interview and thereby reduced inaccuracies in recall. The number of potential study patients selected each month varied according to the interviewers' schedules and the backlog of subjects from the previous month.

We then reviewed the medical records of potential subjects to verify documentation of an acute, symptomatic UTI, which was defined as the presence of dysuria. Dysuria, in turn, was defined as an increased frequency or urgency of urination for 2 weeks or less. We excluded women whose index culture was obtained during treatment for a previously diagnosed UTI or who had asymptomatic bacteriuria within the past year. The remaining women were eligible for interview.

We randomly selected women to serve as control subjects from GHC enrollment files who were matched to cases by date of birth (within 2 years). We reviewed available automated data to eliminate women who had a record of a UTI diagnosis or who had a urine culture that grew 10^5 colonies or more of a uropathogenic organism per milliliter of urine during the preceding month.

After securing permission from the primary care physician, we sent each potential participant a letter describing the study, informing her that we would call her to schedule an interview and providing instructions on how to decline participation. Potential study subjects and controls who had not requested exclusion were contacted by telephone to make a final determination of their eligibility and willingness to participate. We made up to 10 attempts to reach each individual. When contacted, we asked potential participants whether they had received materials about the study and verified that they had been active members of GHC for the past year and did not reside in a nursing home. We eliminated women who did not meet these eligibility criteria as well as those who no longer lived in the area. We also eliminated women with severe medical disability, conditions that might interfere with voiding such as a stroke or other neurologic disease, dementia, severe psychiatric disease, known anatomic abnormalities of the urinary tract, a urinary drainage appliance, end-stage renal disease, or active cancer. We then described the study procedures, requested verbal consent, and scheduled an interview with those who agreed to participate.

We performed all interviews by telephone over a 24-month period from 1994 through 1996 with the computer-assisted telephone software Ci3 (Sawtooth Software, Ketchum, Idaho). This data entry software can be programmed to incorporate complex branching logic and can perform automatic range checks as well as examine internal consistency. The

interview was extensively tested and revised before its implementation. During the first and last months of the study, a second interviewer simultaneously recorded responses during 10% of interviews. The 2 interviewers achieved an interrater reliability that exceeded 90% for all items.

For each group of study subjects drawn monthly, we established a "reference date" that was the midpoint of the range of dates on which positive urine cultures were obtained. This date was programmed into the interviewing software and used as the point of reference for all questions relating to the events during the month prior to the UTI. Since we did not perform one-to-one matching, this permitted us to assign a comparable date to case and control subjects and ask them identical questions.

During the interview, we asked subjects about their general health, including the presence of chronic health problems such as diabetes; their obstetric and gynecologic history; and their sexual activity and contraceptive practices. An additional set of questions dealt with urinary habits and included detailed inquiries about continence. Finally, we asked about their history of previous UTI. Up until that point, the interviewer did not know whether the subject was a case or control. This minimized any potential interviewing bias based on case-control status.

Following the interview, all subjects were invited to attend a voluntary clinic visit for additional studies. These visits were conducted after resolution of the index UTI, when the women were completely asymptomatic and had not taken antibiotics for at least 4 weeks. During the clinic visit, we collected urine specimens and swabs of the vaginal introitus for culture to assess potential uropathogen colonization.

All statistical analyses were performed using SAS (SAS Institute Inc, Cary, NC) and STATA (Stata Corporation, College Station, Tex) software packages. Initially, we characterized cases and controls demographically. Bivariate comparisons of selected potential risk factors by case status were tested using *t* tests for continuous variables and χ^2 tests for categorical variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using standard methods. Using factors determined a priori, we created a series of multivariable logistic regression models to predict odds of UTI.

RESULTS

A total of 1193 case and 1270 control subjects met the eligibility criteria for the study interview. Some women could not be contacted and 145 potential case and 283 potential control subjects declined participation. The final proportions of eligible case and control subjects who participated were 82.5% and 71.7%, respectively. The interview was completed by 1810 women (899 cases and 911 controls). Case and control subjects were similar with regard to age, marital status, ethnicity, education, and income (**Table 1**). Controls were more likely than cases to have better self-reported health.

In bivariate analysis adjusting for age, several risk factors previously reported in young healthy women and in older, debilitated women were found to be significantly associated with UTI in this population (**Table 2**). These included sexual activity, history of UTI, diabetes, incontinence, and estrogen supplementation.

The age-adjusted OR for UTI among women who reported regular sexual activity at least once per week compared with those who were less sexually active or reported no sexual activity was 1.43 (95% CI, 1.11-1.84).

Table 1. Subject Characteristics by Case and Control Status*

Characteristic	Cases (n = 899)	Controls (n = 911)	P Value
Age, mean (SD), y	66.1 (6.2)	66.2 (6.3)	.84
Married or living as married	65.4	63.2	.33
Ethnicity			
White	93.2	92.4	.11
African American	2.1	2.5	
Hispanic	1.0	0.6	
Asian	2.3	4.0	
Native American	1.1	0.6	
Other	0.2	0.0	
Highest educational attainment			
<11 Years of schooling	9.8	6.7	.09
High school graduate	31.7	33.7	
Some college or college graduate	43.7	45.7	
Graduate or professional education	14.8	13.9	
Annual household income, \$			
<25 000	32.6	32.1	.96
25 000-50 000	40.1	41.2	
>50 000	14.4	13.8	
Unknown	12.9	12.8	
Self-reported health status			
Poor	1.1	0.7	<.001
Fair	14.4	7.9	
Good	39.9	35.7	
Very good	34.0	38.2	
Excellent	10.6	17.5	

*Values are given as percentage unless otherwise indicated.

Of the case subjects, 87% reported at least 1 previous UTI compared with only 60% of controls (age-adjusted OR, 4.58; 95% CI, 3.61-5.81). Moreover, 118 (13.1%) reported having diabetes. Of these, 91 were receiving oral medications, insulin treatment, or both. Of the controls, 62 (6.8%) reported having diabetes. Of these, 38 were receiving pharmacological treatment. The age-adjusted OR for patients treated for diabetes was 2.59 (95% CI, 1.75-3.83). There was no increase in the odds of UTI in women with diabetes who did not receive treatment.

Case subjects were more likely than controls to report episodes of incontinence more frequent than once monthly (age-adjusted OR, 1.74; 95% CI, 1.44-2.10) and incontinence with typical quantities greater than a few drops (age-adjusted OR, 1.71; 95% CI, 1.38-2.11). Infrequent incontinence and incontinence of only a few drops were not associated with increased odds of UTI.

Approximately 40% of women reported taking oral estrogen supplementation during the month prior to their entry into the study. Of these women, 97% were prescribed either esterified estrogen (Estratab; Solvay, Brussels, Belgium) or conjugated estrogens. The daily dose of estrogen varied but the modal dose was 0.625 mg/d and the maximum dose was 2.5 mg/d. Most women were instructed to take their estrogen 20, 25, or 30 days per month. Women with an average daily dose greater than 0.625 mg/d were at increased risk for UTI compared with women not taking estrogen therapy (OR, 1.93; 95% CI, 1.23-3.04). Lower doses of estrogen were not associated with increased or decreased UTI risk.

Table 2. Bivariate Age-Adjusted Odds Ratio With Selected Variable for Urinary Tract Infection

Variable	No. of Cases	No. of Controls	Age-Adjusted OR (95% CI)	P Value
Sexual activity				
None	524	554	Referent	
<1/wk	138	162	0.91 (0.70-1.18)	.48
≥1/wk	202	152	1.43 (1.11-1.84)	.005
History of UTI				
No	114	362	Referent	
Yes	784	548	4.58 (3.61-5.81)	<.001
Treatment for diabetes				
None/diet	808	872	Referent	
Oral medication/insulin	91	38	2.59 (1.75-3.83)	<.001
Incontinence frequency				
None/infrequent	480	605	Referent	
>Monthly	418	303	1.74 (1.44-2.10)	<.001
Incontinence amount				
None/few drops	559	661	Referent	
>Few drops	299	207	1.71 (1.38-2.11)	<.001
Average dose of oral estrogen				
None	519	533	Referent	
<0.625/d	133	134	1.02 (0.78-1.34)	.88
0.625/d	177	193	0.94 (0.74-1.20)	.64
>0.625/d	60	32	1.93 (1.23-3.04)	.004

Abbreviations: CI, confidence interval; OR, odds ratio; UTI, urinary tract infection.

Table 3. Multivariable Logistic Regression Model With Selected Variables for Urinary Tract Infection

Variable	OR (95% CI)	P Value
Age	1.01 (1.00-1.03)	.14
Sexual activity		
None	Referent	
<1/wk	0.93 (0.70-1.24)	.63
≥1/wk	1.42 (1.07-1.87)	.01
History of UTI		
No	Referent	
Yes	4.20 (3.25-5.42)	<.001
Treatment for diabetes		
None/diet	Referent	
Oral medication/insulin	2.78 (1.78-4.35)	<.001
Incontinence frequency		
None/infrequent	Referent	
>Monthly	1.36 (1.03-1.78)	.03
Incontinence amount		
None/few drops	Referent	
>Few drops	1.18 (0.88-1.59)	.26
Average dose of oral estrogen		
None	Referent	
<0.625/d	0.94 (0.69-1.27)	.69
0.625/d	0.81 (0.62-1.06)	.13
>0.625/d	1.61 (0.99-2.63)	.006

Abbreviations: CI, confidence interval; OR, odds ratio; UTI, urinary tract infection.

We constructed a series of multivariable logistic regression models based on a priori hypotheses about potential risk factors. In the final model, 5 variables continued to be associated with an elevated risk of UTI: sexual activity, a history of UTI, diabetes, incontinence, and estrogen supplementation (**Table 3**). As in younger women,

sexual activity once per week or more (OR, 1.42; 95% CI, 1.07-1.87) and a history of UTI (OR, 4.20; 95% CI, 3.25-5.42) were strongly associated with current UTI. As in older, debilitated women, treated diabetes (OR, 2.78; 95% CI 1, 78-4.35) and incontinence more than once per month (OR, 1.36; 95% CI, 1.03-1.78) were associated with UTI. Average oral estrogen replacement dosage greater than 0.625 mg/d was more common among women with UTI (OR, 1.61; 95% CI, 0.99-2.63).

Escherichia coli was the infecting organism in 82.0% of women in the case group. The remaining infections were caused by *Klebsiella* species (5.0%), *Proteus* species (3.6%), group B *Streptococcus* (2.7%), *Enterococcus* (2.6%), and a variety of other organisms (4.2%).

During the voluntary follow-up clinic visit, 269 case subjects (29.9%) and 194 controls (21.3%) provided samples for culture of urine and vaginal flora (n=454). These visits were conducted after resolution of the index UTI at a time when the women were completely asymptomatic and had not taken antibiotics for at least 4 weeks. Case subjects were significantly more likely than controls to have *E coli* isolated from their urine and vaginal fluid (OR, 2.2; 95% CI, 1.3-4.0 and OR, 1.7; 95% CI, 1.2-2.6, respectively).

COMMENT

This study investigated potential risk factors for UTI among generally healthy community-dwelling women aged between 55 and 75 years. We found that the factors predisposing these women to UTI reflect the health status of women as they transition toward old age.

The generally accepted risk factors for UTI in young women include sexual activity, use of spermicidal agents and/or contraceptive diaphragm, and a prior history of UTI.^{4,5} In healthy postmenopausal women, sexual activity continues to be a significant albeit less important risk factor regarding the magnitude of effect. Sexual activity less than once per week was not associated with UTI risk. Only women who reported sexual activity once or more per week were at increased risk. Sexual activity of greater frequency was less common and could not be fully assessed. In this population where most women are postmenopausal, the use of spermicidal agents was infrequent. A history of previous UTI is also an important risk factor for current UTI in young women.^{4,5} This factor continued to be associated with UTI risk as women age, suggesting a biologic predisposition independent of behavioral patterns such as sexual activity or contraceptive practice.

As in older, debilitated women, incontinence appears to be an important risk factor for UTI in healthy postmenopausal women. We queried women about frequency of urination and typical amounts of urine loss. In bivariate analysis both were strongly associated with case status. However, in our multivariable models, only incontinence with a frequency greater than once monthly remained a significant risk factor for UTI. The amount of urine lost was no longer independently associated with UTI risk.

Patients with diabetes have a higher risk of asymptomatic bacteriuria, UTI, and pyelonephritis.¹⁶⁻¹⁸ In our

study population, treated diabetes was associated with a higher risk of acute symptomatic UTI. There was no increase in the odds of UTI in women with diabetes who did not receive treatment. A detailed analysis of diabetes and risk of UTI from this study has been described by Boyko et al.¹⁷

Estrogen therapy has been advocated to prevent recurrent UTI.⁹ This recommendation follows 2 randomized trials of intravaginal estrogen, which found a significant risk reduction in recurrent UTI.^{10,11} One trial was double-blind and involved topical estriol cream and the other was an open study of an estrogen-impregnated ring. There were too few women using intravaginal estrogen in our study population to assess the presence of an association with this exposure.

The effect of oral estrogen is less clear. One early randomized trial of 40 women found a positive result, but only after 4 weeks of treatment.¹⁵ A more recent, larger randomized trial did not demonstrate a protective effect.¹² Two recent observational studies reported mixed results.^{2,7} In our patient population, oral estrogen did not reduce the risk of UTI. In the multivariable model, there was a nonsignificant trend toward increased risk of UTI among women taking greater than 0.625 mg/d of oral estrogen (OR, 1.61; 95% CI, 0.99-2.63). Brown et al² in the Heart and Estrogen/Progestin Replacement Study also reported a trend toward increased UTI frequency among women treated with oral estrogens (OR, 1.16; 95% CI, 0.99-1.37). The reasons for a possible discrepant effect between oral and topical replacement therapy are unknown. In our patient population, it is possible that sexually active women or women with a history of UTI may have been treated with estrogens as a preventive measure, which could confound the relationship between oral estrogen and UTI. Additional prospective studies are warranted to more fully understand the effects of oral and intravaginal estrogen therapy on the risk for UTI.

Escherichia coli was the infective agent in 82% of acute UTI in our patient population. This resembles the predominance of *E coli* seen in younger women, in contrast to older, debilitated women who are more commonly infected with other aerobic gram-negative rods. The colonization culture data were collected several weeks after the index infection. We found that cases were still more likely than controls to have both urinary and vaginal colonization with *E coli*, suggesting that chronic colonization with this uropathogen may be a precursor to symptomatic UTI.

We took numerous precautions to minimize potential bias in this population-based study. To prevent misclassification of UTI, we used a case definition (acute urinary symptoms plus a culture yielding 10⁵ microorganisms per milliliter or more), which is more than 95% specific for this diagnosis,¹⁹ and we confirmed the diagnosis using data from medical records, laboratory files, and patient interviews. We randomly selected representative control subjects from the entire GHC enrollment base in 3 counties rather than narrowly selecting from patients visiting a particular clinic or hospital. Exclusion criteria were applied identically to case and control participants.

Interviewing cases as soon as possible after the incident UTI minimized recall bias. Reliability among in-

interviewers was high, and the computer-assisted interview was designed to minimize interviewer errors with built-in branching logic and range checks. Data entry errors were also minimized by this data collection approach. We kept the interviewers uninformed about the subjects' status as cases or controls until the end of the interview, when exposure data were collected and entered into the computerized interviewing program.

Since the study population was insured and mainly white, the results may not be generalizable to other groups of women. The case-control design of this study limits conclusions about possible causal relationships between the exposures of interest and our outcome (UTI). In addition, there may have been additional differences between case and control groups that could contribute to an increased risk for UTI.

In summary, this study is the first large case-control study of risk factors for UTI among generally healthy postmenopausal women. The findings suggest that women in this age group have a risk profile that resembles a transition between young healthy women living in the community and older, debilitated women in institutional settings. Sexual activity, history of UTI, treated diabetes, and incontinence all appear to increase a woman's risk for UTI. Oral estrogen supplementation was not found to reduce the risk of UTI. Prospective studies are needed to delineate more clearly the relationships between these potential risk factors and UTI in this large and growing segment of the population.

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REFERENCES

- Schappert SM. *Ambulatory Care Visits to Physician Offices, Hospital Outpatient Departments, and Emergency Departments: United States, 1997*. Hyattsville, Md: National Center for Health Statistics; 1999. Vital and Health Statistics Series 13; No. 1431-1439. DHHS publication (PHS) 2000-1714.
- Brown JS, Vittinghoff E, Kanaya AM, Agarwal SK, Hulley S, Foxman B. Urinary tract infections in postmenopausal women: effect of hormone therapy and risk factors. *Obstet Gynecol*. 2001;98:1045-1052.
- Foxman B, Barlow R, D'Arcy H, Gillespie B, Sobel JD. Urinary tract infection: self-reported incidence and associated costs. *Ann Epidemiol*. 2000;10:509-515.
- Harrington RD, Hooton TM. Urinary tract infection risk factors and gender. *J Genit Specif Med*. 2000;3:27-34.
- Hooton TM, Scholes D, Hughes JP, et al. A prospective study of risk factors for symptomatic urinary tract infection in young women. *N Engl J Med*. 1996;335:468-474.
- Shortliffe LM, McCue JD. Urinary tract infection at the age extremes: pediatrics and geriatrics. *Am J Med*. 2002;113(suppl 1A):55S-66S.
- Foxman B, Somsel P, Tallman P, et al. Urinary tract infection among women aged 40 to 65: behavioral and sexual risk factors. *J Clin Epidemiol*. 2001;54:710-718.
- Greendale GA, Lee NP, Arriola ER. The menopause. *Lancet*. 1999;353:571-580.
- Raz R. Hormone replacement therapy or prophylaxis in postmenopausal women with recurrent urinary tract infection. *J Infect Dis*. 2001;183(suppl 1):S74-S76.
- Raz R, Stamm WE. A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. *N Engl J Med*. 1993;329:753-756.
- Eriksen B. A randomized, open, parallel-group study on the preventive effect of an estradiol-releasing vaginal ring (Estring) on recurrent urinary tract infections in postmenopausal women. *Am J Obstet Gynecol*. 1999;180:1072-1079.
- Cardozo L, Benness C, Abbott D. Low dose oestrogen prophylaxis for recurrent urinary tract infections in elderly women. *Br J Obstet Gynaecol*. 1998;105:403-407.
- Cardozo L, Lose G, McClish D, Versi E, de Koning Gans H. A systematic review of estrogens for recurrent urinary tract infections: third report of the Hormones and Urogenital Therapy (HUT) Committee. *Int Urogynecol J Pelvic Floor Dysfunct*. 2001;12:15-20.
- Hextall A, Cardozo L. The role of estrogen supplementation in lower urinary tract dysfunction. *Int Urogynecol J Pelvic Floor Dysfunct*. 2001;12:258-261.
- 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.
- Stapleton A. Urinary tract infections in patients with diabetes. *Am J Med*. 2002; 113(suppl 1A):80S-84S.
- Boyko EJ, Fihn SD, Scholes D, Chen CL, Normand EH, Yarbro P. Diabetes and the risk of acute urinary tract infection among postmenopausal women. *Diabetes Care*. 2002;25:1778-1783.
- Patterson JE, Andriole VT. Bacterial urinary tract infections in diabetes. *Infect Dis Clin North Am*. 1995;9:25-51.
- Stamm WE, Counts GW, Running KR, Fihn S, Turck M, Holmes KK. Diagnosis of coliform infection in acutely dysuric women. *N Engl J Med*. 1982;307:463-468.