

## A PROSPECTIVE STUDY OF RISK FACTORS FOR SYMPTOMATIC URINARY TRACT INFECTION IN YOUNG WOMEN

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### ABSTRACT

**Background** Although acute urinary tract infections are common in young women, the associated risk factors have not been defined prospectively.

**Methods** We recruited sexually active young women who were starting a new method of contraception at a university health center or a health maintenance organization (HMO) and monitored them for six months for symptomatic urinary tract infections. Daily diaries and serial interviews were used to collect data on potential risk factors.

**Results** Among 796 women, the incidence of urinary tract infections per person-year was 0.7 in the university cohort (mean age, 23 years; n=348) and 0.5 in the HMO cohort (mean age, 29; n=448). In both cohorts, there were strong dose-response relations between the risk of infection and both recent use of a diaphragm with spermicide (respective relative risks for one, three, and five days of use in the past week, 1.42, 2.83, and 5.68 in the university cohort,  $P<0.001$ ; and 1.29, 2.14, and 3.54 in the HMO cohort,  $P=0.04$ ) and recent sexual intercourse (respective relative risks for one, three, and five days with intercourse in the past week, 1.37, 2.56, and 4.81 in the university cohort,  $P<0.001$ ; and 1.24, 1.91, and 2.96 in the HMO cohort,  $P=0.002$ ). The risk of acute infection was also associated with a history of recurrent infection (relative risk, 5.58 in the university cohort and 2.10 in the HMO cohort) but not with cervical-cap use, ABO-blood-group nonsecretor phenotype, or delayed postcoital voiding.

**Conclusions** Among sexually active young women the incidence of symptomatic urinary tract infection is high, and the risk is strongly and independently associated with recent sexual intercourse, recent use of a diaphragm with spermicide, and a history of recurrent urinary tract infections. (N Engl J Med 1996;335:468-74.)

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**A**N estimated 7 million episodes of acute cystitis occur annually in the United States,<sup>1</sup> and the annual costs of caring for these infections in young women are thought to exceed \$1 billion.<sup>2</sup> Thus, improved means of preventing acute cystitis could lead to important reductions in both morbidity and health care costs. Factors that may influence the risk of urinary tract infection include recent sexual intercourse,<sup>3-7</sup> use of a

diaphragm with spermicide,<sup>4-9</sup> delayed postcoital mic-turition,<sup>4,7,10,11</sup> and the ABO-blood-group nonsecretor phenotype.<sup>12-14</sup> However, these factors have been identified primarily in small case-control studies reporting widely varying risk estimates. Furthermore, questions about the comparability of the groups used in these studies and the potential for recall bias and measurement errors are important limitations of retrospective studies. In addition, all of these recent studies have been conducted in college students, and the findings in these women may not apply to other young women. As yet, there have been no prospective studies large enough to address independent associations between these and other potentially modifiable risk factors and urinary tract infection. We therefore conducted a prospective study using daily diaries to avoid recall bias and to seek more conclusive evidence of risk factors that predispose young women to urinary tract infection. Our main objectives were to determine the incidence of urinary tract infection in two populations of young women and to identify factors independently associated with an increased risk of urinary tract infection in these women.

### METHODS

#### Study Design

This study was conducted at the University of Washington Student Health Center and the Group Health Cooperative of Puget Sound. The University of Washington Student Health Center provides primary care for approximately 85 percent of the 34,000 students enrolled in the university. The Group Health Cooperative is a staff-model health maintenance organization (HMO) located in western Washington. The age, sex, and racial distributions of the approximately 370,000 enrollees are similar to those of the surrounding community.<sup>15</sup>

Subjects were eligible for inclusion in the study if they were healthy women between 18 and 40 years old, were about to start or had started within 6 weeks of enrollment a new method of contraception, had not used this method in the previous 3 months, and had had no more than one urinary tract infection in the previous 12 months. Subjects were ineligible if they were pregnant or planned to become pregnant within the next 6 months, if they had a chronic illness requiring medical supervision, if they had

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used systemic antimicrobial agents within the previous 14 days, or if they had a known anatomical or functional abnormality of the urinary tract.

At the University of Washington, potentially eligible women were referred to the study nurse by the family-planning counselor. Most such women had not started their new method of contraception at the time of study enrollment and began it at the initial visit with the study nurse. At the Group Health Cooperative, potentially eligible women were identified through a review of an automated pharmacy data base.<sup>16</sup> Eligible subjects were sent letters of invitation, contacted by telephone, and if they agreed to participate, scheduled for a clinic visit. Many of these women had begun their new method of contraception at the time of their enrollment in the study. For both groups of women, the starting date of the study was considered to be the date of enrollment.

The study was approved by the University of Washington and Group Health Cooperative human-subjects review committees, and all subjects gave written informed consent.

### Evaluation of Subjects

At the initial visit, all subjects were interviewed with a standardized questionnaire and submitted a midstream urine specimen for evaluation of bacteriuria and pyuria as well as blood and saliva for blood typing and determination of ABO-blood-group secretor status. At both sites, the subjects were provided with a daily diary and instructions to indicate in the diary the days on which the following occurred: sexual intercourse; use of contraception, with the type indicated; postcoital voiding within one hour of coitus; and vaginal and urinary symptoms. The university subjects were asked to return to the clinic for a directed history taking, diary review, and urine culture each month or whenever urinary symptoms developed during follow-up. The HMO subjects were seen every two months for a history taking and midstream urine collection. At the initial visit, the HMO subjects were also instructed in the use and handling of Oxoid dipslides (Unipath, Ogdensburg, N.Y.). At each clinic visit, the diary was examined by the research nurse to encourage compliance. In alternate months, each subject was interviewed by telephone to collect information about episodes of urinary tract infection since the last visit, and she was asked to return a urine dipslide to the clinic for the determination of bacteriuria. The HMO subjects were asked to see their primary care providers for evaluation and treatment if they had urinary symptoms. Subjects at both sites were followed for six months.

### Laboratory Studies

Midstream urine specimens for cultures of aerobic bacteria were collected from the subjects according to previously described methods.<sup>17</sup> The microbiologic procedures used to isolate and identify organisms from urine cultures have also been described previously.<sup>17</sup> ABO-blood-group secretor status was determined in a blinded fashion according to standard methods.<sup>18</sup>

### Definition of Urinary Tract Infection

Subjects were considered to have a culture-confirmed urinary tract infection if they had dysuria, frequency, or urgency (or all three) and  $\geq 10^2$  colony-forming units of a uropathogen per milliliter of midstream urine.<sup>19</sup> Subjects were considered to have a probable urinary tract infection if they had dysuria, frequency, or urgency (or all three) and they had been given a diagnosis of a urinary tract infection by their provider in the absence of a urine culture or, in the absence of provider documentation of a urinary tract infection, there was documentation of treatment with a urinary antimicrobial agent.

### Statistical Analysis

Only subjects who returned to the clinic for at least one follow-up visit were included in the analyses. Except where specified, cul-

ture-confirmed and probable urinary tract infections were combined for analyses. Contraceptive use was based on data reported in the diaries, except oral-contraceptive use, which was assumed to be used daily as prescribed. Because of the differences between subjects at the two study sites, all analyses were conducted separately for women at each site.

Univariate analyses were performed for age, marital status, race or ethnic group, history of urinary tract infections, ABO-blood-group secretor status, and sexual and contraceptive practices. The incidence rates of urinary tract infection were determined by dividing the total number of urinary tract infections during follow-up by the total number of person-years at risk.

Multivariate analyses of the risk of urinary tract infection were based on data reported in the diaries for the frequency of both contraceptive use and intercourse. The Cox proportional-hazards model<sup>20</sup> was used to determine the relative contribution of various factors to the risk of urinary tract infection. We used the counting-process formulation of the Cox model<sup>21</sup> in order to include multiple urinary tract infections per woman, and we used the robust variance correction of Lin<sup>22</sup> to control for possible correlations within subjects. Time zero for the Cox model was taken to be the beginning of the study, and real calendar time was used as the time scale for all analyses. A woman was considered not to be at risk for a new urinary tract infection for five days after the diagnosis of a urinary tract infection.

**TABLE 1. CHARACTERISTICS OF THE STUDY SUBJECTS WHO MADE AT LEAST ONE FOLLOW-UP VISIT.\***

CHARACTERISTIC AT ENROLLMENT	UNIVERSITY	HMO
	SUBJECTS (N = 348)	SUBJECTS (N = 448)
	percent	
Age		
18–22 yr	62	11
23–30 yr	31	49
31–40 yr	7	40
Marital status		
Married	10	61
Never married	85	30
Other	4	9
Race or ethnic group		
White	79	88
Black	2	6
Asian or Pacific Islander	10	3
Other†	9	3
History of any urinary tract infection	28	58
History of $\geq 2$ urinary tract infections	14	38
ABO-blood-group secretor	75	76
Contraceptive method started at study enrollment		
Oral contraceptive	52	29
Diaphragm and spermicide	30	46
Cervical cap	15	15
Spermicide alone‡	3	9

\*Because of rounding not all categories total 100 percent.

†This category includes Native Americans, Hispanics, and other groups.

‡Spermicide alone refers to the use of spermicide in the absence of a diaphragm or cervical cap.

**TABLE 2.** INCIDENCE OF URINARY TRACT INFECTION ACCORDING TO SELECTED CHARACTERISTICS.\*

CHARACTERISTIC	UNIVERSITY SUBJECTS (N=348)			HMO SUBJECTS (N=448)		
	NO. OF PERSON-YR	NO. OF URINARY TRACT INFECTIONS	INCIDENCE PER PERSON-YR OF EXPOSURE	NO. OF PERSON-YR	NO. OF URINARY TRACT INFECTIONS	INCIDENCE PER PERSON-YR OF EXPOSURE
Age						
18-22 yr	92	61	0.7	20	10	0.5
23-30 yr	45	35	0.8	86	44	0.5
31-40 yr	9	2	0.2	70	28	0.4
Marital status						
Married	15	7	0.5	109	36	0.3
Never married	126	88	0.7	52	32	0.6
Other	5	3	0.6	15	14	0.9
Race						
White	116	84	0.7	156	68	0.4
Nonwhite	31	14	0.5	21	14	0.7
History of urinary tract infection						
No previous urinary tract infections	107	53	0.5	74	21	0.3
1 urinary tract infection in lifetime	20	12	0.6	36	16	0.4
≥2 urinary tract infections in lifetime	20	33	1.6	64	42	0.7
ABO-blood-group secretor						
Yes	109	74	0.7	131	59	0.4
No	37	24	0.6	40	22	0.6
Oral-contraceptive use†	75	33	0.4	49	18	0.4
No. of days with intercourse in past 7 days†						
0	40	10	0.2	54	6	0.1
1	30	14	0.5	42	18	0.4
2	26	17	0.6	27	19	0.7
3-7	36	45	1.2	26	25	1.0
No. of days diaphragm and spermicide used in past 7 days†						
0	108	56	0.5	116	44	0.4
1	12	5	0.4	18	12	0.7
2	7	7	1.0	9	7	0.8
3-7	6	18	3.0	6	5	0.8
No. of days cervical cap used in past 7 days†						
0	121	74	0.6	136	59	0.4
1	4	5	1.2	5	3	0.6
2	4	6	1.5	3	0	0.0
3-7	4	1	0.2	3	6	2.0
No. of days spermicide alone used in past 7 days†						
0	124	79	0.6	136	53	0.4
1-7	9	7	0.8	12	15	1.2

\*For comparison, the incidence among women who were taking oral contraceptives; did not have intercourse or use a diaphragm and spermicide, a cervical cap, or spermicide alone in the past 7 days; and had a history of one or fewer urinary tract infections was 0.05 (20.8 person-years) in the university cohort and 0.09 (11.8 person-years) in the HMO cohort.

†This information was obtained from the subjects' diaries. The categories marked with a dagger are not mutually exclusive.

## RESULTS

### Characteristics of the Study Population

A total of 363 university women and 456 HMO members were enrolled in the study, and of these, 348 (96 percent) and 448 (98 percent), respectively, made at least one follow-up visit. Overall, there were

146 person-years of follow-up in the university cohort and 177 person-years in the HMO cohort. The women enrolled in the HMO were older (mean age, 29 years, vs. 23 years in the university cohort), more likely to be married, more likely to be white, more likely to have had a previous urinary tract infection, and more likely to be starting contraception with a

diaphragm and spermicide or with spermicide alone at study enrollment (Table 1). Diary information was complete for 98 percent of the follow-up days in the university cohort and 97 percent of the follow-up days in the HMO cohort. University women reported a median of 6.4 episodes of sexual intercourse per month, as compared with a median of 5.0 in the HMO cohort.

#### Incidence of Urinary Tract Infections

Ninety-eight urinary tract infections (range, 0 to 3 per subject) occurred in the university cohort, as compared with 82 (range, 0 to 7 per subject) in the HMO cohort. Eighty-eight (90 percent) of the urinary tract infections among the university cohort were culture-confirmed, as compared with 49 (60 percent) among the HMO cohort. The incidence of urinary tract infections (culture-confirmed or probable infections) was 0.7 per person-year of follow-up in the university cohort and 0.5 in the HMO cohort. *Escherichia coli* was the only pathogen or a co-existing pathogen in 127 of the culture-confirmed urinary tract infections (93 percent). The rates of urinary tract infection according to selected characteristics are shown in Table 2.

#### Multivariate Analyses

Qualitatively, the results of multivariate models for the university cohort and HMO cohort were remarkably similar. Thus, for ease of comparison, we fit the same model to each study population separately and present the results for categorical variables in Table 3 and for continuous variables in Figure 1. Only women with complete data on all the covariates of interest were included in the multivariate models. As a result, 86 of 98 urinary tract infections in the university cohort and 66 of 82 urinary tract infections in the HMO cohort were included in the multivariate models.

Recent diaphragm and spermicide use, recent sexual intercourse, and a history of recurrent urinary tract infection were independent risk factors for urinary tract infection among women at each study site (Table 3 and Fig. 1). In both cohorts, use of a diaphragm with spermicide had a strong association and dose-response relation with the risk of urinary tract infection (relative risks for one, three, and five days of use in the past week were, respectively, 1.42, 2.83, and 5.68 in the university cohort,  $P < 0.001$ ; and 1.29, 2.14, and 3.54 in the HMO cohort,  $P = 0.04$ ). Similarly, there was a strong association and a dose-response relation between recent sexual intercourse and the risk of urinary tract infection (relative risks for one, three, and five days with intercourse in the past week were, respectively, 1.37, 2.56, and 4.81 in the university cohort,  $P < 0.001$ ; and 1.24, 1.91, and 2.96 in the HMO cohort,  $P = 0.002$ ). A history of recurrent urinary tract in-

**TABLE 3.** RELATIVE RISK OF URINARY TRACT INFECTION, AS DETERMINED BY FITTING SEPARATE COX MODELS FOR EACH COHORT.\*

COVARIATE	RELATIVE RISK (95% CI)	P VALUE
<b>HMO cohort†</b>		
Married	0.44 (0.25–0.75)	0.002
History of $\geq 2$ urinary tract infections at study entry	2.10 (1.23–3.57)	0.006
Any use of spermicide alone in past 7 days	3.24 (1.63–6.47)	$< 0.001$
<b>University cohort‡</b>		
Married	0.48 (0.21–1.13)	0.09
History of $\geq 2$ urinary tract infections at study entry	5.58 (3.24–9.63)	$< 0.001$
Any use of spermicide alone in past 7 days	0.77 (0.38–1.55)	0.47

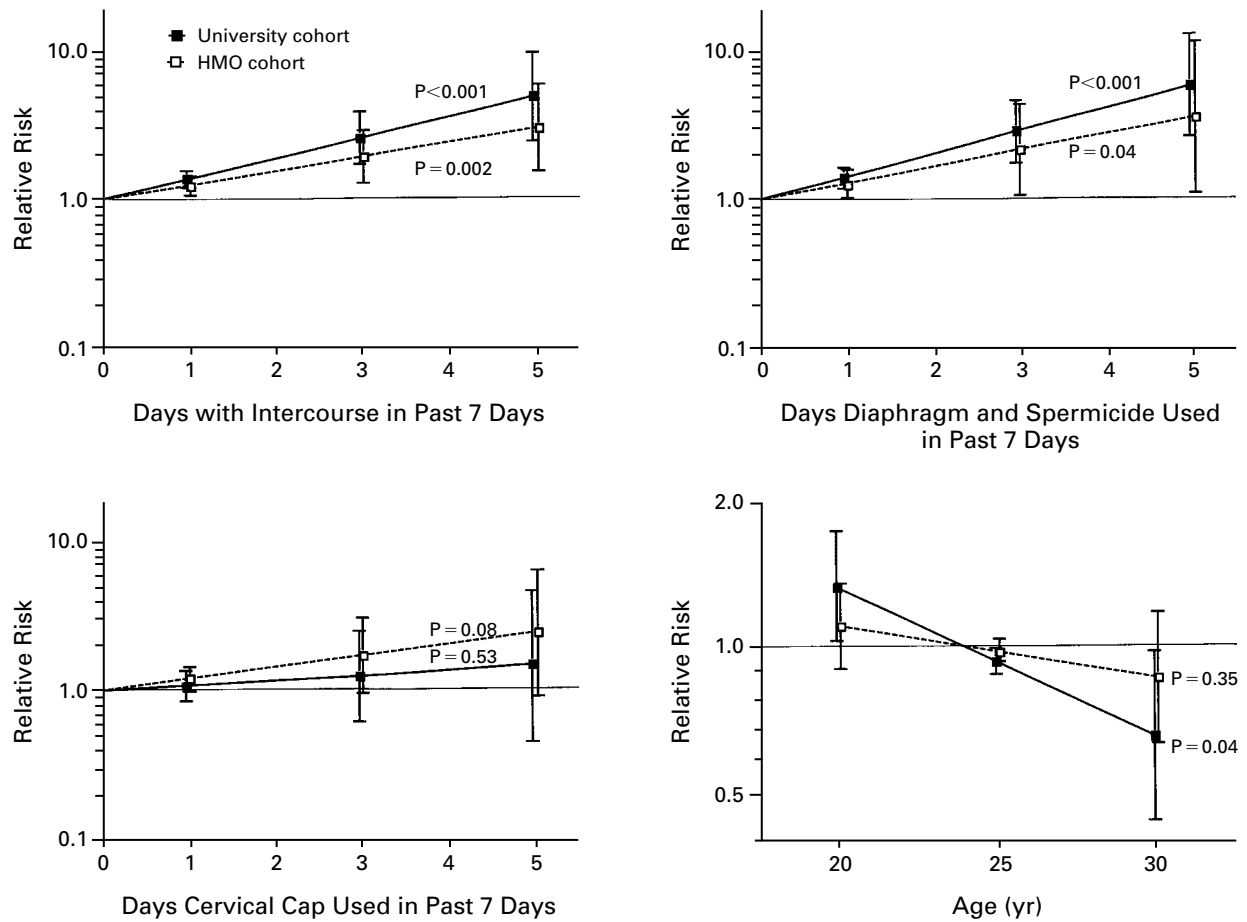
\*Additional covariates in the model are given in Figure 1. CI denotes confidence interval.

†The analysis included only the 66 urinary tract infections in women who used oral-contraceptive pills, a diaphragm with spermicide, a cervical cap, or spermicide alone and who provided diary information.

‡The analysis included only the 86 urinary tract infections in women who used oral-contraceptive pills, a diaphragm with spermicide, a cervical cap, or spermicide alone and who provided diary information.

fection was also strongly associated with the risk of urinary tract infection (relative risk, 5.58 in the university cohort and 2.10 in the HMO cohort;  $P < 0.001$  and  $P = 0.006$ , respectively). Increasing age was associated with a reduced risk of urinary tract infection in each cohort but was significantly related only in the university cohort (Fig. 1). Similarly, being married was associated with a reduced and almost identical relative risk in both cohorts, but the reduction in risk was statistically significant only in the HMO cohort ( $P = 0.002$ ) (Table 3), primarily because so few of the university women were married (Table 1). Use of a cervical cap did not have a statistically significant association with the risk of urinary tract infection. Although there was a trend in both cohorts toward an increased risk with frequent cap use (Fig. 1), this association approached statistical significance only in the HMO cohort ( $P = 0.08$ ).

The only important difference between the two study groups in terms of risk factors for urinary tract infection involved the use of spermicide alone as the contraceptive method of choice. In the university cohort, spermicide use in the past week had no significant effect on the risk of urinary tract infection, whereas in the HMO cohort, spermicide use in the past week significantly increased the risk of urinary tract infection ( $P < 0.001$ ) (Table 3). Because of the small number of women in these cohorts who used spermicide alone as their contraceptive, we were unable to estimate a dose-response effect of spermicide



**Figure 1.** Relative Risk of Urinary Tract Infection, as Determined by Fitting Separate Cox Models for Each Study Site for the Continuous Variables of Age, Days of Diaphragm Use with Spermicide in the Past Seven Days, Days with Sexual Intercourse in the Past Seven Days, and Days of Cervical-Cap Use in the Past Seven Days.

The bars indicate the 95 percent confidence intervals. Additional covariates in the model are given in Table 3.

as we did with the use of a diaphragm with spermicide, cervical cap, and intercourse.

Other potential risk factors, including blood-group secretor status, race or ethnic group (white vs. other), parity, time of voiding after intercourse, and having a new sexual partner since the last visit, were not statistically significant when added to the model shown in Table 3 and Figure 1 ( $P > 0.20$  for each variable at each site).

#### Multivariate Analyses with Only Culture-Confirmed Urinary Tract Infections

Using the model shown in Table 3 and Figure 1, we repeated the analyses using only the subgroup of patients with culture-confirmed urinary tract infections. These analyses yielded essentially the same results as those described above (data not shown), except that in the HMO cohort, the relative risk associated with a history of recurrent urinary tract in-

fection decreased from 2.1 in the full analysis to 1.4 in this subanalysis ( $P = 0.25$ ).

#### DISCUSSION

The overall incidence of symptomatic urinary tract infections in the two populations studied was 0.5 per person-year in the HMO cohort and 0.7 per person-year in the university cohort. Although the incidence among the young, largely unmarried university students was higher than among the older, largely married HMO members, the difference was not dramatic and suggests that neither the incidence of nor risk factors for urinary tract infection seen in university women are unique. We are not aware of other prospective studies with which these incidence data can be compared. Although the HMO population at the Group Health Cooperative is representative of all women in the Puget Sound region,<sup>15</sup> our study subjects were not randomly selected and had

**TABLE 4.** PREDICTED RELATIVE RISK OF URINARY TRACT INFECTION FOR A 24-YEAR-OLD UNMARRIED WOMAN FROM THE UNIVERSITY COHORT BASED ON THE MODEL IN TABLE 3 AND FIGURE 1.\*

NO. OF DAYS WITH INTERCOURSE IN THE PAST 7 DAYS	NO. OF DAYS DIAPHRAGM AND SPERMICIDE USED IN THE PAST 7 DAYS				
	0	1	2	3	4
	relative risk of urinary tract infection				
0	1.0	1.4			
1	1.4	1.9			
2	1.9	2.6	3.8		
3	2.6		5.1	7.3	
4	3.5				14.1
5	4.8				
6	6.6				
7	9.0				

\*Although the model can predict the risk for any arbitrary number of days with intercourse and contraceptive use, only cells for which we have at least 365 person-days of data are filled in. A lifetime history of more than one urinary tract infection multiplies the relative risk by 5.6. A qualitatively similar pattern is seen in the HMO cohort, although the relative-risk estimates are somewhat smaller (Table 3 and Fig. 1).

to meet specific enrollment criteria. Therefore, our incidence data cannot be readily generalized to the population at large. However, given that in 1990 approximately 53 million adolescent girls and women 15 to 44 years old reported being sexually experienced in the United States,<sup>23</sup> our incidence data suggest that urinary tract infections in young women constitute a major source of morbidity and health care costs that may have been considerably underestimated by information based on office visits.<sup>1</sup>

In previous prospective studies of the relation between sexual intercourse and bacteriuria, Nicolle et al. found that 15 of 19 episodes of bacteriuria (79 percent) developed within 24 hours of intercourse,<sup>3</sup> whereas Kunin et al. found no association between coital frequency and the presence of bacteriuria.<sup>24</sup> However, both studies were small, neither controlled for other possible risk factors such as contraceptive method, and both used bacteriuria rather than symptomatic infection as an end point. Several case-control studies have also demonstrated an association between coital frequency and the risk of urinary tract infection.<sup>4,5,8</sup> Our prospective study confirms the results of both Nicolle et al.<sup>3</sup> and these case-control studies in that we found a strong independent association and a dose-response relation between sexual intercourse and the risk of urinary tract infection. For example, our model (Table 3 and Fig. 1) predicts that an unmarried, 24-year-old female university student who has had sexual intercourse without a diaphragm and spermicide on three of the

past seven days has a risk of urinary tract infection that is 2.6 times greater than that of a similar student who has not had intercourse in the previous week; if she had had intercourse daily for the past week, the risk of urinary tract infection would be 9 times greater (Table 4).

The use of a diaphragm with spermicide has been associated with an increased risk of urinary tract infection in several retrospective case-control studies.<sup>4-9</sup> Our results confirm these earlier findings by demonstrating the independence of this association and, as with sexual intercourse, by demonstrating a strong dose-response relation between the use of a diaphragm and spermicide and the risk of urinary tract infection. Our finding that spermicide use alone was associated with urinary tract infection in the HMO cohort is consistent with the results of our previous studies, which showed that exposure to spermicides increased the risk of vaginal colonization<sup>14</sup> and bacteriuria<sup>25</sup> with *E. coli*, but not to the degree seen with the use of a diaphragm and spermicide. Spermicides probably increase the risk of urinary tract infection by altering the vaginal environment in favor of colonization with uropathogens, thus predisposing women who use these products to urinary tract infection.<sup>26</sup>

This study also addressed the relation of cervical-cap use to urinary tract infection. Although we did not find that use of the cervical cap (even though it is usually used in conjunction with spermicidal jelly) was significantly associated with urinary tract infection, there was a trend in this direction in both study cohorts and, with a larger sample, a significant effect may have been detected. The weaker association of urinary tract infection with cervical-cap use may reflect the fact that less spermicide is used with the cap than with the diaphragm and it is better contained, which may result in less alteration of the vaginal flora and, thus, a lower risk of urinary tract infection.

As in two case-control studies,<sup>4,5</sup> we demonstrated a relation between a history of urinary tract infection and current urinary tract infection. This strong association could reflect a biologic predisposition to urinary tract infection among certain women due to their ABO-blood-group nonsecretor status,<sup>27</sup> an immune hyporesponsiveness to *E. coli* antigens,<sup>28</sup> or other factors. Alternatively, persistent abnormalities in the vaginal microflora, resulting from either a prior infection or prior antimicrobial therapy,<sup>29</sup> or behavioral factors could underlie this association. Of these factors, our data suggest that the nonsecretor phenotype is not independently associated with an increased overall risk of sporadic urinary tract infection in women. However, there were too few recurrent urinary tract infections in the study to allow us to determine the association of recurrent infection with nonsecretor status or other factors. Further studies

are needed to ascertain the basis for recurrent urinary tract infection in young women.

The conclusions and generalizability of our findings are strengthened by the prospective study design,<sup>30</sup> the daily recording of information of interest, the high follow-up rate over the six-month period of observation, and the similarity of the findings in two different groups of women, one of which is representative of the population in the Puget Sound region. Further studies should address how sexual and contraceptive practices might be modified in young women to decrease the associated risk of urinary tract infection.

Supported by grants (DK 40045 and DK 47549) from the National Institute of Diabetes and Digestive and Kidney Diseases (to Dr. Stamm).

*We are indebted to Elaine Henley, M.D., and Elaine Jong, M.D., medical directors, Kathleen Slettebak, Ingrid Helsel, R.N., and the staff at Hall Health Center for helping with patient enrollment; to Natalie DeShaw for assistance with patient care and data collection at Hall Health Center; and to Cathy Hutchison, Darlene White, Sarah McElroy, Jane Grafton, Patty Karlen, Fae Newmann, Wendy Bensussen-Walls, Sandy Howard, Lillie Stevens, Mary Fors, and Joyce Burgess for helping with patient enrollment and data collection at the Group Health Cooperative.*

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