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Clinical implications of the anatomical position of the urethra meatus in women with recurrent post-coital cystitis: a case-control study

Kostis Gyftopoulos[1,2] ⬤ · Miltos Matkaris[2] · Aikaterini Vourda[3] · George Sakellaropoulos[4]

Abstract

Introduction and hypothesis Recurrent post-coital urinary infection (rUTI)—usually cystitis—is a common entity among otherwise healthy young women. However, little is known about the possible influence of genital anatomical variations. Only a shorter urethral meatus-anus distance has been described as a risk factor. The aim of this study was to evaluate our hypothesis that a shorter urethra-vagina distance is involved in the etiology of post-coital urinary infection.

Methods In this prospective case-control study, 61 young women aged between 18 and 40 years with an acute post-coital UTI and a history of intercourse-related rUTI were consecutively recruited between January 2013 and February 2018. Fifty-six age-matched, sexually active women with no history of UTI served as controls. Perineal measurements included the distances between the clitoris-urethra (C-U), urethra-vagina (U-V), urethra-anus (U-A) and perineum. Demographic and sexual behavior characteristics and the morphology of the urethral meatus were also noted. Univariate analysis compared variables between groups. ROC analysis was used to define the efficiency of perineal measurements in predicting outcome. Odds ratios and 95% confidence intervals for UTI-predisposing variables were estimated using logistic regression analysis.

Results The U-V and U-A distance was shorter in patients compared with controls [median (interquatile range): 16 mm (14–18) vs. 21 mm (19–23) and 51 mm (47–53) vs. 59 mm (55–62), respectively, $p < 0.001$]. The U-V performed better in ROC analysis than the U-A distance (AUC 0.952 vs. 0.875, $p = 0.023$). The only statistically significant parameters in multivariate analysis influencing UTI were BMI (OR: 0.702; 0.510–0.967, $p = 0.030$) and U-V (OR: 0.297; 0.161–0.549, $p < 0.001$).

Conclusions Our results indicate an association between shorter urethra-vagina distance and post-coital rUTIs.

Keywords Anatomy · Cystitis · Female · Meatus · Urethra · Recurrent UTI

Introduction

Urinary tract infection (UTI) is a common morbidity among women worldwide; it has been estimated that the risk for a woman to acquire a UTI in her lifetime is over 50% [1]. Recurrent infections (rUTIs), defined as more than two episodes over a 6-month period or more than three during a year, may occur in up to 25% of these cases, accounting for an increased burden in morbidity and socioeconomic costs [2, 3]. In young, otherwise healthy women, rUTIs are commonly limited to recurrent cystitis often associated with sexual intercourse, hence the term "post-coital cystitis." Behavioral factors that may influence the incidence of rUTIs in this setting include use of condoms or spermicides, frequency of intercourse and number of sexual partners [4]. However, the importance of these and other non-behavioral factors [e.g., body mass index (BMI)] is still debatable. In recent years, research has been focused on the virulence of certain uropathogens (mainly *E. coli* strains) and their interaction with host susceptibility factors [5–8].

It is generally accepted that the main route of infection is a fecal-perineal-urethral route, which may involve intermediate steps of periurethral or vaginal colonization of the responsible

✉ Kostis Gyftopoulos
kogyftop@yahoo.gr

1 Department of Anatomy, University of Patras Medical School, Patras, Greece

2 Olympion Hospital, Patras, Greece

3 Department of Microbiology, University of Patras Medical School, Patras, Greece

4 Department of Medical Physics, University of Patras Medical School, Patras, Greece

microbiota [1]. During sexual intercourse, the male partner is a "passive" tool that facilitates inoculation and advancement of uropathogenic bacteria through the urethra meatus. It is therefore striking that there is a paucity of studies regarding the local anatomical factors that may facilitate this ascending infection. A shorter urethra-anus distance (although marginal) has been the only putative contributing anatomical factor [9]. On the other hand, we have proposed the hypothesis that low placement of the urethral meatus toward the vaginal opening is the actual causal factor of post-coital UTI due to increased friction by penile thrusts during intercourse [10].

The aim of this study was to evaluate the external genital anatomy of young women with a history of intercourse-related rUTIs and compare this with a control group with similar demographic and sexual behavior characteristics. Our working hypothesis was that a shorter urethra-vagina distance may play a greater role than the urethra-anus distance in recurrent post-coital infections.

Materials and methods

Population selection

Case subjects (incident cases) were prospectively recruited to this study from January 2013 to February 2018 and included young, otherwise healthy women aged between 18–40 years visiting as outpatients with an acute post-coital UTI episode <u>and</u> a history of rUTI (as defined in the Introduction) related to sexual intercourse. The episode was considered post-coital when symptoms commenced within 24 h after sexual intercourse, and only culture-confirmed UTIs were included. Women with a recent history of sexually transmitted diseases (STD), history of voiding dysfunction, history of pregnancy and vaginal delivery, previous pelvic or genital surgery, diabetes, multiple sex partners or practicing anal intercourse were excluded before recruitment. The control group consisted of consecutive cases of sexually active women of similar age with no history of UTI or other morbidities attending the clinic for unrelated reasons (usually a regular gynecological visit). Control cases were recruited between March 2017 and February 2018, and similar exclusion criteria applied. The study protocol was designed according to the Declaration of Helsinki, and Ethics/Institutional Review Board approval was obtained.

To determine the sample size and statistical power, we performed preliminary analysis using the freely available statistical software G*Power. Due to the lack of similar studies available in the literature, we performed a pilot study of ten cases and ten controls (subsequently included in the study) to determine the urethra-vagina (U-V) distance differences. Based on these initial measurements (observed difference of means:

4 mm; SD of measurements: 6 mm), a sample size of 43 subjects in each group was needed for a statistical power of 90% and $\alpha = 0.05$.

Data collection

After informed consent was obtained, the demographic, medical and sexual characteristics were recorded, including age, BMI, UTIs during the past year, age at first UTI, average weekly frequency of sexual intercourse during the past 3 months and contraceptive measures (condom-diaphragm/spermicide-oral contraceptives/"pill").

Measurements

The subjects were placed in the lithotomy position and asked to relax as possible. With the aid of a disposable tape measure, the following distances were recorded (in mm): clitoris-urethra (C-U), urethra-upper limit of introitus (U-I), urethra-fourchette (U-F) and perineum (P) (Fig. 1a). The term "perineum" was used in its clinical sense, defined as the length of the area between the fourchette and the anal opening. The *base* of the clitoris (i.e., the upper point of the clitoral body, immediately under the clitoral hood) was chosen over the clitoral glans as a reference point, as the length of the clitoris varies among individuals. For the urethral and anal opening, the *center* of each opening was used as the reference point during measurements, in accordance with the practice of similar measurements of the genital hiatus and perineal body, as established by the International Continence Society [11]. Since the vaginal opening or introitus is a rather irregular opening, the "urethra-vagina" (U-V) distance was calculated using the formula: [(U-F) − (U-I)] divided by 2. The urethra-anus distance was calculated as the sum of (U-F) + (P). All measurements were performed by the two primary investigators (K.G. and M.M.). The measurement method was developed and jointly tested in initial patients of all ages (not included in the study) to eliminate interobserver variability. To avoid bias due to patient anxiety or movement, three set of measurements were taken, and the average value was finally recorded. Moreover, the appearance and position of the urethral meatus was noted. The meatus was assigned "clear" when it was easily identifiable between the clitoris and introitus (Fig. 1b, c). The term "skin tags" was used when the meatus was hidden under skin tags or hymenal remnants and not easily identifiable without the aid of a tip of a 10-French Nelaton catheter or cotton swab (Fig. 1d–f). The term "hypospadias" was used when the actual urethral opening was cranial to the vaginal opening, located at the interior vaginal wall. Specific

Fig. 1 **a** Landmarks for external genitalia measurements used in this study: 1: base of clitoris; 2: center of urethra meatus; 3: upper limit of introitus (hymen at 12 o'clock); 4: fourchette; 5: center of anal opening. **b**–**c** Easily identifiable, clear urethral meatus. **d**-**f** "Skin tags" covering the urethral meatus. (meatus position shown with arrows and cotton swab in **f**)
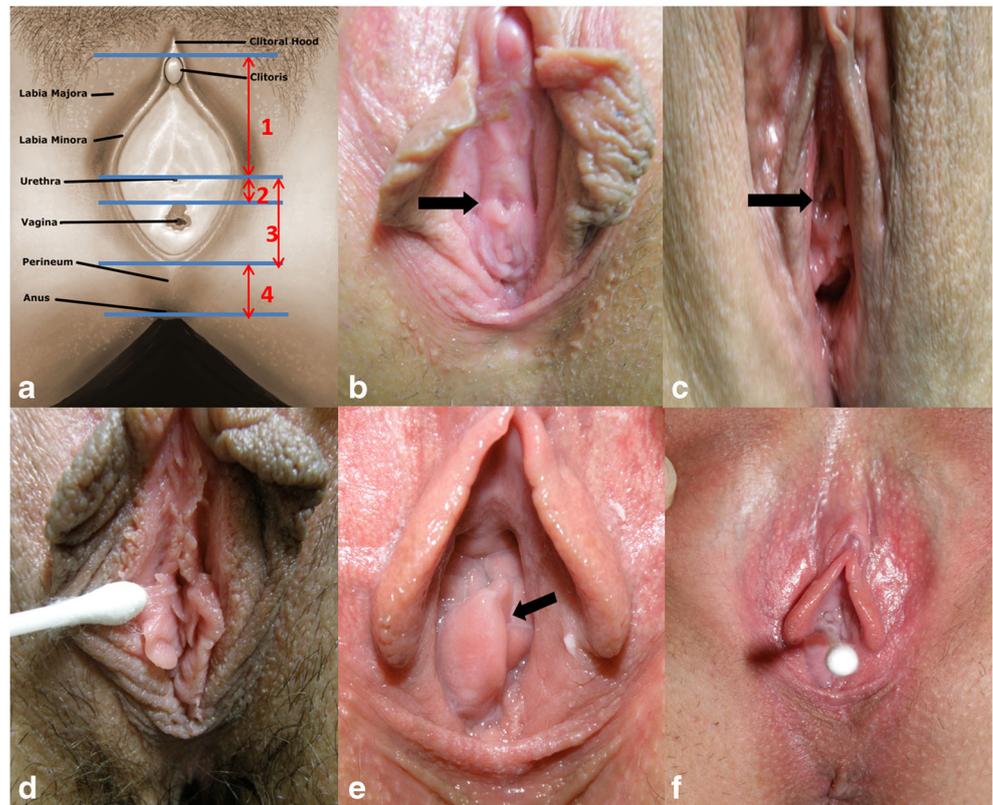
written informed consent for publication was obtained by patients photographed for illustrative purposes.

Data analysis

Statistical analysis was performed using the IBM SPPS v.23 statistics software. All continuous variables were checked for normality using the Kolmogorov-Smirnov test, and Mood's median test was subsequently performed. Fischer's exact test was used for nominal variables. We further investigated the diagnostic sensitivity and specificity of each variable pertaining to perineal measurement using ROC analysis. Finally, we developed binary logistic regression analysis models to evaluate the predictive ability of each variable

within a multivariate approach. $p < 0.05$ was considered significant.

Results

Sixty-one cases with rUTI and 56 control subjects were included during the study period. The demographic, medical and sexual behavior characteristics are presented in Table 1. The two groups were comparable in terms of age, BMI and contraceptive/prophylaxis measures. None of the subjects used a diaphragm/spermicide as a contraceptive method. The control group appeared to have more frequent sexual

Table 1 Demographic and sexual behavior characteristics of subjects

	Patients ($n = 61$)	Control ($n = 56$)	p value	Test
Age (years)*	25 (21–28)	24 (22–27)	0.772	Median test
BMI*	22.4 (19.8–23.9)	22.4 (20.7–24.3)	0.820	Median test
Sex/week*	2 (2–3)	3 (2–4.75)	0.005	Median test
Condom use	31	28	1.000	Fisher's exact
OC/"pill" use	4	11	0.051	Fisher's exact
UTI past year*	3 (3–4)			
Age at first UTI*	20 (19–22)			

*Median (interquartile range, 25%–75%)

Table 2 Measured genital distances and urethra meatus morphology. All measurements are presented in mm, rounded to integer values, according to measurement precision (1 mm)

	Patients (n = 61)	Control (n = 56)	*p* value
Clitoris-urethra*	31 (28–34)	28 (25–30)	0.047
Urethra-introitus*	10 (9–12)	12 (10–14)	< 0.001
Urethra-fourchette*	22 (19–24)	30 (25–35)	< 0.001
Urethra-vagina*	16 (14–18)	21 (19–23)	< 0.001
Perineum*	30 (28–31)	26 (19–30)	0.004
Urethr-anus*	51 (47–53)	59 (55–62)	< 0.001
Urethra morphology: clear/skin tags	37/24	50/6	0.0005**

*Median (interquartile range, 25%–75%). Mood's median test

**Fischer's exact test, two-sided

intercourse than the patients, and the difference was statistically significant (Table 1).

We further evaluated possible differences of BMI between patients and controls by stratifying subjects in three categories: normal, overweight (≥ 25) and obese (≥ 30). No statistical significant differences were noted between groups.

Perineal measurements and urethral meatus morphology are shown in Table 2. All studied parameters showed a statistically significant difference between groups. In summary, the urethra was positioned farther from the clitoris and closer to the vaginal and anal opening in patients compared with controls. Interestingly, the median clinical perineum length was longer in the patient group. Concerning the morphology of the urethral opening, 39.66% of patients presented with skin tags surrounding the urethral orifice compared to 10.71% of controls (Fisher's exact test, two-sided *p* = 0.0005). One patient was classified as 'hypospadias' with a clear urethral orifice opening inside the vagina immediately after the hymen.
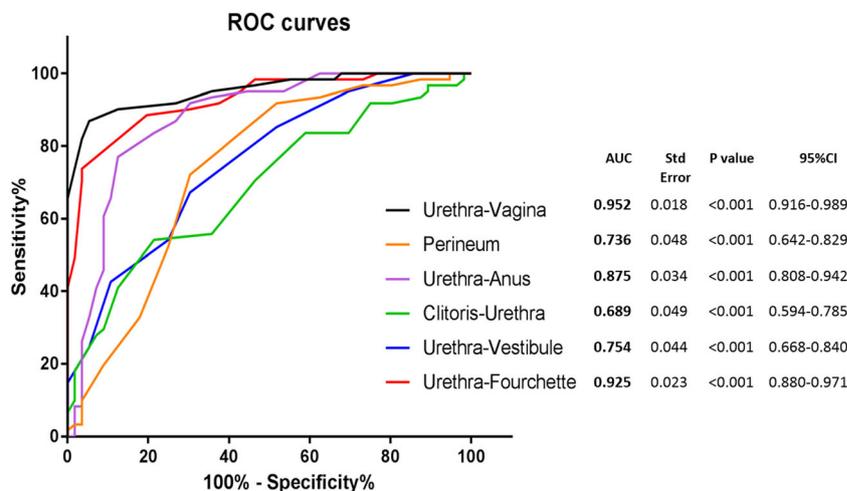
We used ROC analysis to further evaluate the performance of the different perineal measurements according to outcome. The highest area under the curve (AUC) was obtained for the urethra-vagina distance (Fig. 2). We further examined the difference between urethra-vagina and urethra-anus ROC

performance using a Z-test [12], and the difference was statistically significant (*p* = 0.023).

In a third step, we examined the effect of multiple variables on outcome (UTI), developing three binary logistic regression analysis models (forced, forward and backward stepwise) with case-control status as outcomes. The variables used included age, BMI, sex/week, use of a condom/pill, urethral morphology and the urethra-vagina and urethra-anus distances, which were most statistically significant in the univariate analysis. In the forced model, where all variables were included ad hoc, the two variables that reached statistical significance were BMI (OR: 0.702; 95% CI 0.510–0.967, *p* = 0.030) and the urethra-vagina distance (OR: 0.297; 95% CI 0.161–0.549, *p* < 0.001) (Fig. 3). Similar results were obtained with both the forward entry and backward elimination stepwise models (OR: 0.731; 95% CI 0.552–0.968, *p* = 0.029 for BMI and OR: 0.271; 95% CI 0.160–0.458, *p* < 0.001 for U-V).

Based on the significant results for the urethra-vagina distance, we tried to develop a more easily identifiable and measureable parameter for the position of the urethra meatus in relation to the vaginal opening. We named it the "urethra position" and defined it as the ratio of the clitoris-urethra distance to the clitoris-fourchette distance (a and b in Fig. 4).

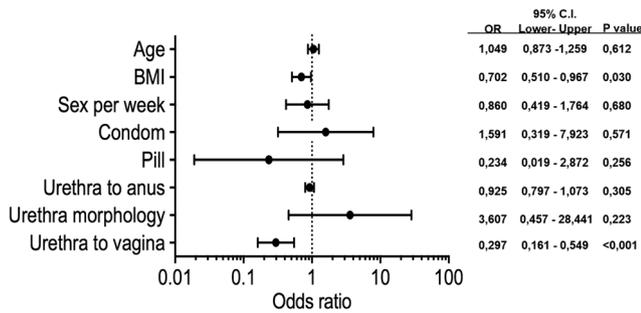**Fig. 2** Comparison of ROC curves for external genitalia measurements

	AUC	Std Error	P value	95%CI
Urethra-Vagina	0.952	0.018	<0.001	0.916-0.989
Perineum	0.736	0.048	<0.001	0.642-0.829
Urethra-Anus	0.875	0.034	<0.001	0.808-0.942
Clitoris-Urethra	0.689	0.049	<0.001	0.594-0.785
Urethra-Vestibule	0.754	0.044	<0.001	0.668-0.840
Urethra-Fourchette	0.925	0.023	<0.001	0.880-0.971

		95% C.I.	
	OR	Lower- Upper	P value
Age	1,049	0,873 -1,259	0,612
BMI	0,702	0,510 - 0,967	0,030
Sex per week	0,860	0,419 - 1,764	0,680
Condom	1,591	0,319 - 7,923	0,571
Pill	0,234	0,019 - 2,872	0,256
Urethra to anus	0,925	0,797 - 1,073	0,305
Urethra morphology	3,607	0,457 - 28,441	0,223
Urethra to vagina	0,297	0,161 - 0,549	<0,001

Fig. 3 Forest plot (log scale) of the estimates of OR for different risk factors for rUTI

We performed ROC analysis of this new variable, and it revealed excellent clinical prediction performance (AUC = 0.932, $p < 0.001$, Fig. 4).

Discussion

The results of this study emphasize the importance of the position of the urethral meatus in relation to the vaginal opening as a predisposing factor for recurrent post-coital cystitis. So far, this finding has not been revealed in the available literature. The classic study of Hooton et al. focused on the distance of the urethra-anus; although the mean difference between groups was limited to 2 mm, this study set the widely accepted notion that a shorter distance may facilitate the migration of uropathogens from the fecal reservoir toward the urethra, predisposing for rUTI [9]. However, the true effect of such a small difference in perineal length on the perineal and periurethral colonization and—eventually—UTI is arguable; the same investigators did not find a significant association between rUTI and activities such as toilet wiping patterns or frequent use of pantyhose and tights, parameters that would reasonably affect the perineal flora [2].

Our initial hypothesis was based on the assumption that sexual intercourse per se may represent a predisposing factor to rUTI if the urethra meatus is closer than "normal" to the

vagina [10]. In our study, the median U-V distance was 5 mm shorter in patients than controls ($p < 0.001$). Although the "traditional" urethra-anus distance was also found to differ statistically in our study group, the U-V distance performed better in the ROC analysis and was the only length variable retained in all three linear regression models (OR: 0.297; 0.161–0.549, $p < 0.001$). Combined with the longer C-U distance in patients, this finding illustrates the frequent lower placement of the urethral meatus in women with rUTI as a possible predisposing factor. We attempted to develop an easy way to identify this low placement as a risk factor for UTI by defining "urethral position" as a percentage of two easily identifiable distances: clitoris-urethra and clitoris-fourchette, the latter often referred to as the "length of labius minus." The test performed well in ROC analysis: a cutoff value of 0.54 corresponds to the highest pair of sensitivity/specificity values (90 and 80%, respectively).

Although no similar studies exist in the literature, our findings in measuring external genitalia are in accordance with perineal measurements in premenopausal women investigated for reasons unrelated to rUTI, mainly for cosmetic genitalia surgery; the referred measurements are essentially comparable to those in our control group [13–16]. Another interesting finding in this study was the differences in the morphology of the meatus, with almost 40% of the patients (versus 10.7% of controls) presenting with "skin tags" around the urethral opening. These skin tags are usually considered hypertrophic hymenal remnants [17]. Older reports of urethro-hymenal fusion depicted a ring of hymenal remnants that would displace the urethral meatus caudally toward the vaginal opening [18]. In the past, urethroplasty techniques were advocated for surgical correction of this anatomical entity [18, 19]. In our cases, however, no real urethro-hymenal ring was present; these skin tags were freely mobile, without retracting the meatus. The importance of this observation is obscure; we initially postulated that the uneven morphology of the vestibule might aid the retention of bacteria-laden mucous around the meatus, facilitating a retrograde infection during intercourse.

Fig. 4 Urethra position calculation scheme and ROC curve
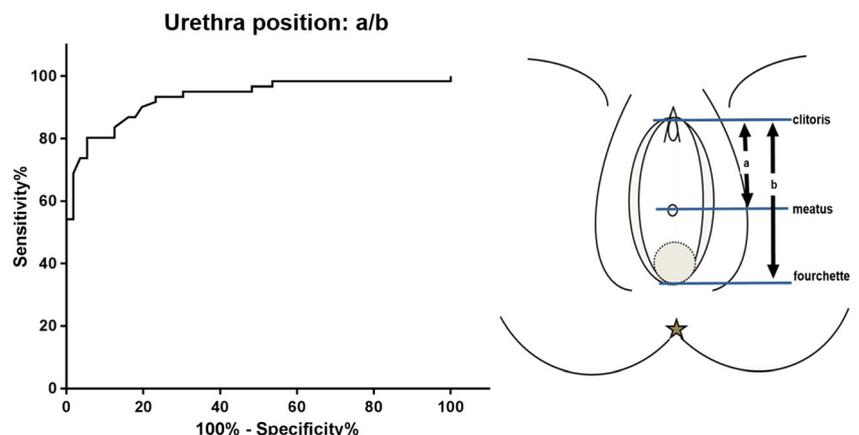
Although this may be a plausible explanation, the morphology of the meatus did not prove an independent factor in the logistic regression models.

Another interesting finding in our study was the appearance of BMI as an independent risk factor for rUTI in the logistic regression models (OR: 0.702; 95% CI 0.510–0.967, $p = 0.030$). The effect of BMI is debatable; most authors agree that BMI does not play an important role [4]. Other studies however have revealed an association of obesity with rUTI in premenopausal women or lower urinary tract symptoms in women over 40 years [20, 21]. Although BMI did not differ between patients and controls, it is possible that increased BMI affects the occurrence of rUTI in undefined ways, possibly by altering the cell-mediated immune responses of the host [20]. It is also worth noting that the widely accepted rUTI risk factor of frequent sexual intercourse was not verified in this study. On the contrary, control subjects had in fact more frequent sexual intercourse than patients (median 3 vs. 2 times weekly, respectively; $p = 0.005$). In multivariate analysis, the frequency of sexual intercourse as an independent risk factor did not reach statistical significance. The discrepancy of our results compared with other studies may lie in the fact that we only recruited women with confirmed intercourse-related UTI and not through a general UTI registry. Moreover, other possibly confounding factors like multiple/new sex partners or anal intercourse were used as exclusion criteria before recruitment.

To the best of our knowledge, this is the first study to propose an anatomical approach to the risk for post-coital cystitis under the mechanics of sexual intercourse. Our results suggest that low positioning of the urethra meatus toward the vaginal opening may be the most important factor associated with this specific setting of rUTI in otherwise healthy young women. A strength of our study is the careful selection of patients in terms of evident post-coital infections and elimination of possible confounding factors, making our sample uniform albeit rather small. A possible limitation may be the ad-hoc power and sample size estimation, which was based on our pilot study measurements. However, we could not use other values as this type of measurement (urethra-vagina) in rUTI patients was unavailable in the existing literature. Concerning the measurements, the two investigators were not blinded to the case-control status of the subjects. However, every effort was made to establish accurate measurements after the initial trial of the methodology; this is the main reason that measurements were taken by the principal investigators themselves and not by an assistant or nurse. Another possible limitation may involve the potential for recall bias related to previous episodes to coitus. We tried to obviate this by prospectively recruiting only women with at least one acute post-coital episode (≤ 24 h from coitus) and insisted on this criterion when taking the history of previous UTIs.

Conclusions

This study provides evidence that a shorter urethra-vagina distance may play an important role in acquiring recurrent UTIs related to sexual intercourse for otherwise healthy young women. If these findings are verified in larger studies, this could represent a paradigm shift in the investigation of the etiopathology and the prevention strategies for this common cause of morbidity in young women.

Compliance with ethical standards

Conflicts of interest   None.

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