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Patolojik Servikovajinal Smearler ve İdrar Yolu Enfeksiyonu Arasında Bir İlişki Var mıdır?

Is There an Association Between Pathologic Cervicovaginal Smears and Urinary Tract Infection?

Alp Tuna BEKSAÇ [1] Orcid ID:0000-0001-6742-0040
Hanife Guler DONMEZ [2] Orcid ID:0000-0002-7413-4939

[1] Department of Urology, Cleveland Clinic, Cleveland, Ohio, USA
[2] Department of Biology, Faculty of Science, Hacettepe University, Ankara, Turkey

ÖZ

Amaç: Patolojik servikovajinal smearler (anormal sitolojik bulgular, fungal enfeksiyonlar, bakteriyel vajinoz ve enflamasyon) ile idrar yolu enfeksiyonu (İYE) arasındaki ilişkiyi değerlendirmektir.

Gereçler ve Yöntem: 222 hastanın Pap ile boyanmış servikovajinal smearlerini değerlendirdik. Patolojik servikovajinal smearleri olan hastalar çalışma grubu (n = 59, %26,6), smearlerinde patolojik bulgu olmayan 163 (%73,8) hasta ise kontrol grubu olarak kabul edildi. Çalışma ve kontrol grupları İYE varlığı açısından karşılaştırıldı.

Bulgular: Bu kohortta (n = 222), sırasıyla %5,4, %5,9, %8,6 ve %6,8 oranlarında anormal sitolojik bulgular, bakteriyel vajinoz, mantar enfeksiyonu ve enflamasyon olduğu belirlendi. İYE oranı çalışma ve kontrol gruplarında sırasıyla %5,1 ve %3,1 olarak gösterildi (p = 0,441). Anormal sitolojik bulgular, bakteriyel vajinoz, mantar enfeksiyonu ve enflamasyon varlığı ayrı ayrı değerlendirildiğinde mantar enfeksiyonu olan hastalarda kontrollere göre İYE anlamlı olarak daha sık bulundu (p = 0,039).

Sonuç: Mantar enfeksiyonu olan hastalarda İYE'nin daha sık olduğu bulunmuştur.

Anahtar Kelimeler: İdrar yolu enfeksiyonu, bakteriyel vajinozis, mantar enfeksiyonu, enflamasyon, servikovajinal smear

ABSTRACT

Aim: To evaluate the association between pathologic cervicovaginal smears (abnormal cytological findings, fungal infections, bacterial vaginosis, and inflammation) and urinary tract infection (UTI).

Materials and Method: We evaluated Pap-stained cervicovaginal smears of 222 patients. Pathologic cervicovaginal smears were accepted as a study group (n = 59, 26.6%) while the remaining 163 (73.8%) patients who had no pathologic smears were accepted as a control group. Study and control groups were compared in terms of the presence of UTI.

Results: In this cohort (n = 222), we have demonstrated abnormal cytological findings, bacterial vaginosis, fungal infection, and inflammation with rates of 5.4%, 5.9%, 8.6%, and %6.8, respectively. The rate of UTI was demonstrated to be 5.1% and 3.1% in the study and control groups, respectively (p = 0.441). When the presence of abnormal cytological findings, bacterial vaginosis, fungal infection, and inflammation were considered separately, UTI was found to be significantly more frequent in patients with fungal infection compared to controls (p = 0.039).

Conclusion: UTI was found to be more frequent in patients with fungal infection.

Key words: Urinary tract infection, Bacterial vaginosis, fungal infection, inflammation, cervicovaginal smear

INTRODUCTION

Urinary tract infections (UTIs) are considered to be the most common bacterial infection. According to the 1997 National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey, UTI accounted for nearly 7 million office visits and a million emergency department visits, resulting in 100,000 hospitalizations (1). Women are significantly more likely to experience UTI than men. Nearly one in three women will have had at least one episode of UTI requiring antimicrobial therapy by the age of 24 years. Almost half of all women will experience one UTI during their lifetime (2).

Specific subpopulations at increased risk of UTI include infants, pregnant women, the elderly, patients with spinal cord injuries and/or urinary catheters, patients with diabetes or multiple sclerosis, patients with acquired immunodeficiency disease syndrome/human immunodeficiency virus, patients with underlying urologic abnormalities and women with lower genital tract infections such as Bacterial vaginosis (BV) (3–7).

Vaginal flora is a critical site for the development of UTIs, due to including infector and protector factors (8,9). The balance between these factors is crucial in maintaining healthy flora (10). BV is the most common vaginal infection in women with a rate of %8-75. It develops due to imbalanced overgrowth of Gardnerella vaginalis and other BV-related microorganisms (11). BV is related

Sorumlu Yazar/ Corresponding Author:
Hanife Guler DONMEZ
Department of Biology, Faculty of Science, Hacettepe University, Ankara-TURKEY
E-mail: hnftnr@gmail.com

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to miscarriage, preterm labor, low-birth-weight infants, chorioamnionitis, postpartum endometritis, and post-abortion pelvic inflammatory disease as well as UTIs (12,13). Fungal infection is the second most common infection after BV and is diagnosed in up to 40% of women with gynecological complaints (13,14). Inflammation is commonly demonstrated at the Pap-stained cervicovaginal smears in clinical practice. The prevalence of inflammation differs between one population to the other one (7.6% to 80.5%) (15,16). Abnormal cytological findings include atypical squamous cells of undetermined significance (ASCUS), atypical squamous cells, low-grade squamous intraepithelial lesion (LSIL), and high-grade squamous intraepithelial lesion (HSIL). Human papillomavirus (HPV) is the main cause of these cytopathological findings (17). There was no previous study investigating the relationship between these changes and UTIs.

The aim of this study was to understand whether or not UTI is associated with pathologic cervicovaginal smear results.

MATERIALS AND METHOD

We evaluated cervicovaginal smears of 222 women between September 2018 and April 2020 at the Department of Obstetrics and Gynecology, Hacettepe University. All of the required demographic and clinical data as well as laboratory results including detection of UTI were obtained from the electronic database of our institution (Table 1).

Table 1. Demographic and clinical characteristics of the study population

	Urinary tract infection (–) (n = 214)	Urinary tract infection (+) (n = 8)	Total (n = 222)	p
Age (mean±SD)*	39.24±11.65	40.75±15.19	39.29±11.76	0.723
Gravidity (mean±SD)†	2.20±2.00	3.25±2.25	2.23±2.01	0.095
Parity (mean±SD)†	1.43±1.18	2.12±0.99	1.46±1.17	0.051
Abortus (mean±SD)†	0.50±1.28	0.25±0.46	0.50±1.26	0.798

*: Student t-test, †: Mann Whitney-U test, p>0.05, SD: Standard deviation

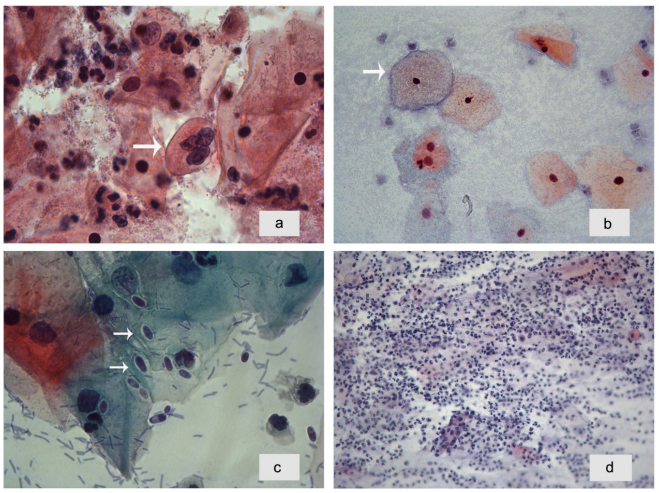
This cross-sectional study was approved by the Hacettepe University Ethics Committee (reference number GO18/915-34) and it was conducted by the Declaration of Helsinki. Written informed consent was obtained from all individual participants included in this study.

Patients having clinical complaints (dysuria, pollakiuria, and costovertebral region sensitivity) and urination problems were asked to have urine analysis and culture. Patients with at least 2 positive cultures (≥ 100 000 colony forming units (CFU) per milliliter (ml)) were accepted as UTI and included to this study. Antibiograms were obtained in all cases to determine antimicrobial resistance and to choose the ideal antibiotics for the treatment. Patients with immune system disorders were excluded from the study. Escherichia coli, Klebsiella pneumoniae, Streptococcus haemolyticus, and Enterococcus faecalis were the microorganisms responsible for the UTIs.

Papanicolaou staining method

Cervicovaginal samples were smeared on a slide and immediately fixed with ethanol (96%). Fixed slides were immersed in the decreasing level of alcohol (85% to 50%) to distilled water. Rehydrated slides were stained with Harris' Hematoxylin (Merck, Germany) for 2 min. and rinsed under running tap water. Hydrochloric acid-alcohol (%1, v/v) was used for decoloring. After washing the slides with distilled water and increasing alcohol series (50% to 85%), Orange G and EA 65 dyes (Merck, Germany) were performed, respectively. To clean off the excess dye, slides were washed with 95% ethanol after each staining step. The stained smears were immersed in Xylene 15 min., then Entellan (Merck, Germany) was used as a mounting medium. The cytological findings were investigated by light microscopy and photographed using a camera attached-light microscope (Leica DM 4000B) (Figure 1)

Figure 1. Cytological findings (a,d); a: A hyperchromatic, multinuclear cell indicates abnormal cytological findings (arrow) (×400), b: A clue cell covered by bacteria indicates BV (arrow) (×400), c: Several yeasts with uncolored cell walls show fungal infection (arrows) (×1000), d: Inflammation (×400), Papanicolaou staining.



Cervicovaginal samples were examined with regard to the presence of microorganisms, epithelial cell abnormalities, and other non-neoplastic findings according to Bethesda 2014 (18).

Statistical analysis

The statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 23). Data were presented as number, percentage, and mean ± standard deviation (SD). Categorical data were compared using the Chi-square test or Fischer's exact test. In numerical data (age, gravida, parity, and abortus), the normality analysis was performed with the Shapiro-Wilk test. Non-parametric "Mann Whitney-U" and "Kruskal Wallis-H" tests were used for comparison non-normally distributed groups, however, student t-test was used for normally distributed data. Statistical limit of significance was accepted as $p < 0.05$.

RESULTS

Cervicovaginal smears (n = 222) were obtained from patients between the ages of 20 and 76 years (39.29±11.76). Pathologic smear results were accepted as a study group (n = 59, 26.6%), while remaining 163 (73.8%) patients who had no abnormal cytological findings, fungal infection, BV, and inflammation were accepted as a control group. In this cohort (n = 222), we found abnormal cytological findings (n =12), BV (n =13), fungal infection (n = 19), and inflammation (n = 15) with rates of 5.4%, 5.9%, 8.6%, and %6.8, respectively (Table 2).

Table 2. The frequencies of urinary tract infection in this cohort

(–) n, (%)	Urinary tract infection		Total
	(–) n, (%)	(+) n, (%)	
Negative	158 (73.8)	5 (62.5)	163 (73.4)
Abnormal cytological findings	12 (5.6)	0 (0.0)	12 (5.4)
BV	13 (6.1)	0 (0.0	13 (5.9)
Fungal inf	16 (7.5)	3 (37.5)	19 (8.6)
Inflammation	15 (7.0)	0 (0.0	15 (6.8)
Total	214 (100)	8 (100)	222 (100)

In this cohort (n = 222), we demonstrated that 8 of 222 (3.6%) patients had UTIs. As seen in Table 3, the rate of UTI was demonstrated to be 5.1% and 3.1% in the study and control groups, respectively (p = 0.441) (Table 3).

Table 3. Rate of urinary infection in terms of the presence of abnormal epithelial cells, BV, fungal infection, inflammation

	UTI (+) n, %	UTI (–) n, %	*p*
Control group (negative smear results)	**5 (3.1)**	**158 (96.9)**	0.441
Study group (pathologic smear results)	**3 (5.1)**	**56 (94.9)**	
Abnormal epithelial cells (+)	0 (0.0)	12 (100)	0.698
Abnormal epithelial cells (–)	5 (3.1)	158 (96.9)	
BV (+)	0 (0.0)	13 (100)	0.678
BV (–)	5 (3.1)	158 (96.9)	
Fungal infection (+)	3 (15.8)	16 (84.2)	0.039*
Fungal infection (–)	5 (3.1)	158 (96.9)	
Inflammation (+)	0 (0.0)	15 (100)	0.641
Inflammation (–)	5 (3.1)	158 (96.9)	

*:p<0.05, Fisher's exact test

When the presence of "abnormal cytological findings", "BV", "fungal infections", and "inflammation" were considered separately, UTI was found to be significantly more frequent in patients with fungal infection compared to controls (15.8% vs. 3.1%, p = 0.039).

DISCUSSION

Generally, UTI is identified as microbial infiltration of the normally sterile urinary tract and infection of the kidneys, ureters, urethra, and bladder (19). Women are more susceptible to UTI than men, due to short urethra, lack of prostatic secretion, pregnancy, menopause (low estrogen levels), contraception methods such as diaphragms, and easy contamination with feces (19,20). UTIs are treated by antibiotics, but 27% had recurrence within the following six months, and a second recurrence over the same period with a rate of 2.7% (21). Thus, understanding the predisposing factors behind UTI is therefore of high clinical significance in developing an effective treatment for the disease. Thus, we aim to understand the association between pathologic smear results (including abnormal epithelial cells/infections) and the presence of UTI.

The link between UTIs and vaginal microbiome has been widely investigated and three possible models have been proposed. In the first model, the vagina can serve as a reservoir for uropathogens especially E. coli. In the second model, vagina consists of various microorganisms which are also uncommon uropathogens. Finally, vaginal bacteria increase the susceptibility of UTIs via affecting the cellular structures in the bladder (8,22). On the other hand, vaginal microbiota can frequently be identified in urine because of vaginal contamination. The exact mechanism behind UTI is still a matter of debate.

Studies generally focused on the relationship between BV and UTI. Harmanli, et al., reported that UTIs was found in women with and without BV with rates of 22.4% and %9.7, respectively. BV was reported to be significantly associated with an increased risk of UTIs (23). According to Gilbert et al., BV-related Gardnerella vaginalis is not a causative agent for UTI, however, it leads to cellular damage on the surface of the bladder and facilitates the E. coli proliferation (13). In this study, we could not demonstrate a statistically significant relationship between the presence of BV and UTIs.

In this study, we have shown that 15.8% of women with fungal infection had UTI (n = 3/19). There is no study showing a direct link between the presence of vulvovaginal fungal infections and UTIs, however, previously reported analysis showed a shift from a healthy vaginal microbiome dominated by L. crispatus to L. iners in vulvovaginal candidiasis (24). Metagenomic analysis of urinary tract infections demonstrated that L. iners can be a causative factor for UTIs (25). Thus, it might be suggested that changes in the vaginal microbiota resulting in the shift of dominant Lactobacillus species increase the risk of UTI.

In this study, we could not demonstrate an association between abnormal cytological findings (ASCUS, LSIL, and HSIL) and UTIs. We also could not show any relationship between inflammation and UTIs. Consistent with our study, there was no previous study demonstrating an association between these two conditions and UTIs.

The main limitation of this study is the limited number of cases and limited information about UTIs. We believe that further studies are necessary related to vaginal microbiota and UTIs.

In conclusion, UTI was found to be more frequent in women with vaginal fungal infection. However, the relationship between fungal infection and UTI is still a matter of debate.

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