

Research Article

Previous antibiotic treatment as a risk factor for recurrent vulvovaginal candidiasis

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Abstract

The incidence of recurrent vulvovaginal candidiasis (RVVC) is extremely high. RVVC is likely to have a greater impact on patients. The aim of the study was to explore the risk factors of recurrent vulvovaginal candidiasis (RVVC) in the tropical coastal area. In this case-control study, a questionnaire survey was conducted in patients with VVC in the Sanya area from July 2014 to December 2016. The data included demographic characteristics, host factors, and behavioural characteristics. According to the maximum number of symptomatic episodes per year, the participants were classified into a non-recurrent VVC (NRVVC; < 4 episodes/year, including the current one) group or a RVVC group (≥ 4 episodes/year, including the current one). Crude odds ratios were calculated for potential risk factors and were adjusted using logistic regression. All vaginal secretions of patients with RVVC were cultured. Of the 728 cases of VVC, 69.0% (502/728) were NRVVC, and 31.0% (226/728) were RVVC. Previous antibiotic treatment (adjusted OR: 4.41, $p < 0.01$), repeat abortion ($p < 0.05$), and vaginal lavage (adjusted OR: 1.62, $p < 0.05$) were significantly associated with RVVC. A total of 230 yeasts isolates were obtained from 226 patients. *C. albicans* were the predominant *Candida* species (194 strains) in all patients of VVC. Our results demonstrate that in the tropical coastal area, a significant association was found between previous antibiotic treatment and incident RVVC. Host factors may be the most important factors in the occurrence of RVVC.

Introduction

Vulvovaginal candidiasis (VVC) is one of the most common gynecological diseases worldwide. Almost 75% of women experience at least one episode of VVC at some point during their lifetime [1]. Acute inflammatory episodes are usually treated with anti-fungal drugs of the azole class. Guidelines from a number of medical associations recommend long-term off label suppressive treatment with an antifungal drug, usually fluconazole, for at least 6 months [2-5]. This treatment regimen can prevent recurrences for the duration of the therapy; however, some studies have reported recurrence rates of 60%–70% within 6 months after cessation of this treatment regimen [4,6,7]. Thus, while these anti-fungal medications are efficacious at treating acute infections, they are unable to prevent recurrences, which usually occur after a few months. Recurrent vulvovaginal candidiasis (RVVC) or complicated VVC is defined as four or more episodes

of microscopically confirmed candidiasis per year [7,8]. Approximately 5% of first-time VVC patients subsequently experience RVVC. Compared to non-recurrent vulvovaginal candidiasis (NRVVC), RVVC is likely to have a large impact on patient's quality of life [9]. Moreover, it consumes a large amount of healthcare resources [10,11]. RVVC pathogenesis involves host factors, behavioral factors, vulvar dermatosis, and microbial factors similar to non-*albicans* *Candida* infections [12]. Host-related factors include pregnancy, uncontrolled diabetes, immunosuppression, antibiotics, glucocorticoid use, and genetic predispositions. Behavioral risk factors include the use of oral contraceptives, intrauterine devices, spermicides, and condoms, and some hygiene, clothing, and sex-related habits. However, few studies have investigated risk factors for VVC in tropical coastal areas, particularly for recurrent infections.

We used a case-control study to explore the risk factors for

More Information

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RVVC in Sanya, focusing on host and behavioral risk factors. Most behavioral factors have little effect on the recurrence of VVC, and host factors may be the most important influencing factors. Previous antibiotic treatment, repeated abortion, and vaginal lavage were found to be significantly associated with RVVC. In addition, the data indicate that showering twice a day may protect women living in tropical areas against recurrence of VVC. These studies may provide some interesting information for clinical treatment and prevention of recurrence of female *Candida* infections in the future.

Patients and Methods

Patients

This was a case control study. Using a detailed questionnaire survey, we collected information from patients visiting the outpatient department of the Hainan branch of General Hospital of People's Liberation Army, Hainan General Hospital, and Sanya Maternity and Child Health Care Hospital between July 2013 and December 2014. We included all patients whose condition was diagnosed as VVC by the attending physician.

The diagnosis of VVC was based on WHO diagnostic criteria, which includes a combination of results of clinical anamnesis, gynecological examination, and microscopic investigation of the vaginal fluid with 10% potassium hydroxide. If no blastospores or (pseudo-) hyphae were observed microscopically, species were identified by culture. According to the number of symptomatic episodes per year, the participants were included in a NRVC group (< 4 episodes/year, including the current one) or a RVVC group (≥ 4 episodes/year, including the current one), and were asked to complete a questionnaire. Because of the wide use of over-the-counter (OTC) antifungal drugs, the history of RVVC was confirmed by at least one previous hospital diagnosis and two self-diagnoses within 1 year. Using the responses to the questions on sexual behavioural characteristics, we excluded asexual and pregnant women from the study.

Vaginal samples

Physicians obtained samples from the lateral vaginal wall with a sterile cotton-tipped swab. The swab was placed in a tube filled with saline prior to direct microscopic examination on a wet slide to which a drop of 10% potassium hydroxide had been added. For NRVC patients with a clinical presentation suggestive of vulvovaginal candidiasis but with negative microscopic investigation results, physicians collected another vaginal swab, which was sent for culture. All specimens of RVVC were sent for culture. Specimens were inoculated into sterile saline and immediately seeded onto plates containing Sabouraud dextrose agar (Biomérieux, France) with 100 mg/ml chloramphenicol, and incubated at 25°C for up to 5 days. Strains were identified using a VITEK 2 Colorimetry yeast identification ID card (Vitek; Biomérieux, France). Because we recruited the patient basing on the initial

diagnosis in the outpatient clinic, the group assignment would be verified again after the result of culture returned. Patients without a history of VVC were excluded from the study if they had negative results on both culture and wet-slide tests.

Questionnaire survey

After a VVC diagnosis had been confirmed clinically, the patients were interviewed by trained nurses using the questionnaire. The nurses and patients were blinded to the group assignment. The data included: (1) demographic characteristics: age, ethnic group, marriage, length of residence in Hainan Island, location of household registration (within or outside Hainan), type of permanent residence registration (urban or rural), location of current address, education, and occupation; (2) host factors: previous antibiotic treatment (≤ 4 weeks earlier), oestrogen replacement therapy or oestrogen-based contraception, comorbidities such as diabetes, nephropathy, heart disease, and HIV infection; (3) behavioral characteristics: childbearing, abortion, contraceptive method, regularity of menstrual cycle, sexual activity during menstrual period, use of sanitary towel, frequency of shower during menstrual period, use of panty liners, frequency of sex, cleaning of vulva before and after sex, number of sexual partners, wearing of tight pants, fabric of underwear, frequency of underwear replacement, methods used for cleaning underwear, methods used for drying underwear, showering frequency, methods used for showering, vaginal lavage, frequency of swimming; and (4) the maximum number of episodes of VVC in a 12-month period.

Ethics

This study was approved by the ethics committee of Chinese PLA General Hospital. All patients signed an informed consent form before participating in the study. No complications occurred after the collection of vaginal samples.

Statistical analysis

Univariate analysis was performed to determine potential risk factors for RVVC. Variables with $p \leq 0.10$ by univariate analyses were included in multivariate analysis. Multivariate analysis was performed using conditional multiple logistic regression for the risk factors associated with RVVC. 2 or Fisher's Exact Test for categorical variables and independent t-test for continuous variables. Adjusted odd ratios were calculated. Two-sided $p < 0.05$ were considered statistically significant. Statistical analysis was performed using IBM SPSS ver. 22.0.

Results

Patient characteristics

A total of 800 patients participated in the questionnaire survey. In the NRVC group, patients with blank or input errors in their questionnaires and negative results on both wet-slide and culture tests were excluded from the study. After



exclusion of invalid cases, 728 valid cases (91%) were included. Of the 728 participants, 502 (69.0%) who experienced VVC < 4 times per year were categorized as NRVVC. The remaining 226 patients (31.0%) were included in the RVVC group. There were no significant differences between the two groups in age, ethnic group, marriage, length of residence on Hainan Island, location of household registration, type of registered permanent residence, type of current address, education, and occupation ($p > 0.05$, date not shown).

Risk factors

Univariate analyses of the data revealed that most host and behavioral characteristics did not differ significantly between the two groups: disease, number of children, contraceptive method, menstrual cycle, sexual activity during menstrual period, use of sanitary towel, use of panty liners, frequency of sex, cleaning of the vulva before and after sex, number of sexual partners, wearing of tight pants, fabric of underwear, frequency of underwear replacement, methods used to clean underwear, methods used for drying underwear, showering frequency, methods used for showering, and frequency of swimming ($p > 0.05$, date not shown). Variables with p values less than or equal to 0.10 in univariate models were examined in multivariate modelling. Because comorbidities, use of panty liners, and contraceptive method were considered potential factors, these variables were included in the multivariate analysis. Table 1 shows the significant results of logistic regression analysis of risk factors. Previous antibiotic treatment, repeated abortion, and vaginal lavage were identified as independent risk factors for RVVC. Moreover, showering twice a day may protect women against recurrence of VVC.

Strain distribution

All RVVC patients' vaginal secretions were cultured. A

total of 230 yeasts isolates were obtained from 226 patients. Two species of *Candida* were isolated from each of 4 patients. However, it's a pity that due to the limitations of laboratory conditions, there were 7 strains failed to identify. There were 3 strains reported as non-albicans *Candida* (NAC). 4 patients of *Candida* mixed only reported two kinds of *Candida* infection. *C. albicans* were the predominant *Candida* species (194 strains, 84.35%) found in all patients of VVC, followed by *C. tropicalis* (9 strains, 3.91%), *C. glabrata* (8 strains 3.48%), *C. parapsilosis* (6 strains, 2.61%), *C. famata* (4 strains, 1.74%) and *C. krusei* (2 strains, 0.87%)

Discussion

Sanya, a tropical coastal city in the southernmost region of China, is located on Hainan Island between 18°09' and 18°37' latitude. With the aggravation of the environmental contamination problem in mainland China, an increasing number of Chinese people travel or relocate to Sanya. VVC is very common in women worldwide, with an estimated 5% of VVC patients experiencing four or more episodes in their lifetime [7]. Moreover, the frequency of RVVC in the general population might be underestimated because of under-reporting. An online omnibus survey that included respondents from the United States and five European countries [13] revealed that less than one third of respondents (28%) reported four or more infections per year. Similarly, in our questionnaire survey, approximately 31% of the patients reported that they had experienced more than four episodes in a 12-month period. Although we did not emphasize the words "recurrent" vaginitis during recruitment of participants for this study. While it is possible that patients with RVVC were more willing to participate in the study, our results might also indicate that the incidence of RVVC is not as low as previously reported, especially in the tropics.

Table 1: Logistic regression analysis of risk factors associated with recurrent vulvovaginal candidiasis.

Variables ^a	RVVC n (%)	NRVVC n (%)	p - value	or	95% CI	
					Lower	Upper
Previous antibiotic treatment (≤ 4 weeks earlier)*			< 0.01			
No (n = 660)	184 (81.4)	476 (94.8)	Reference			
Yes (n = 68)	42 (18.6)	26 (5.2)	< 0.01	4.41	2.50	7.79
Abortion*			0.01			
None (n = 309)	79 (35.0)	230 (45.8)	Reference			
One (n = 196)	56 (24.8)	140 (27.9)	0.73	1.08	0.70	1.68
Two (n = 132)*	50 (22.1)	82 (16.3)	0.02	1.76	1.08	2.86
Three (n = 60)*	28 (12.4)	32 (6.4)	0.00	2.59	1.38	4.88
≥ Four (n = 31)	13 (5.8)	18 (3.6)	0.05	2.42	1.02	5.76
Vaginal lavage*			0.01			
No (n = 457)	127 (56.2)	330 (65.7)	Reference			
Yes (n = 271)	99 (43.8)	172 (34.3)	0.01	1.62	1.12	2.34
Frequency of showering			0.08			
Once/day (n = 541)	178 (78.8)	363 (72.3)	Reference			
≥ Twice/day (n = 74)*	10 (4.4)	64 (12.7)	0.01	0.35	0.16	0.76
Once/2 days (n = 42)	17 (7.5)	25 (5.0)	0.41	1.37	0.65	2.91
Once/3 days (n = 16)	5 (2.2)	11 (2.2)	0.73	0.80	0.22	2.90
Irregularly (n = 55)	16 (7.1)	39 (7.8)	0.75	0.89	0.43	1.82

^aOnly the variables with $p \leq 0.05$ are included
 CI: Confidence Interval; NRVCC: Non-Recurrent Vulvovaginal Candidiasis; RVVC: Recurrent Vulvovaginal Candidiasis
 * $p < 0.05$



The results of the present study suggest that *C. albicans* was the predominant Candida species isolated from cases of RVVC. *Candida tropicalis* was the most frequently isolated non-*albicans* species in patients with RVVC. In recent years, several studies have shown prevalence of *C. albicans* varying from 46.9% to 76.3% [14,15]. Similarly in China, Liu, et al. [16] reported that the rate of isolation of *C. albicans* was decreased during the years 2008 to 2012 compared with the years 2003 to 2007 (88.3% vs 82.2%, $p < 0.01$) [16]. It probably reflects a bias towards more complicated patients in studies conducted in vulvovaginitis clinics. In these studies, the isolates cultured usually originate from patients with refractory VVC or those whose diagnosis has been missed using regular microscopy examination. With the popular use of azoles, many women can obtain VVC treatment without a physician prescription. *C. albicans* is susceptible to most azoles, but most non-*albicans* species are resistant to azoles. So the more non-*albicans* species were found in clinic.

There were no significant differences between the two groups in all demographic characteristics. But in a previous study, the cumulative probability of RVVC was found to be age dependent, reaching 25% for those aged 50 years and older [13]. However, in the present study, patients with RVVC aged older than 50 years accounted for only 3.5% of the total RVVC cases. Moreover, there were no significant differences in patient age between the two groups.

Our results revealed that recent antibiotic treatment was the most important host factor related to the pathogenesis of RVVC. A previous study also indicated that the use of short courses of oral antibiotics could increase the prevalence of asymptomatic vaginal Candida colonization, and consequently, the incidence of symptomatic VVC [17].

China has a high rate of both warranted and unwarranted antibiotic use relative to that in western countries. A study of 230,800 outpatient prescriptions in 28 Chinese cities found that nearly half the prescriptions written between 2007 and 2009 were for antibiotics and that ten percent were for two or more antibiotics [18]. This may be one of the reasons that recent antibiotic use was the most significant factor in the present study [19,20]. However, the results of our study did not confirm the results of previous studies [21,22], which identified host factors related to RVVC development, such as diabetes mellitus, and oral contraceptive and steroid use. One reason for this inconsistency may be the limited number of patients with chronic diseases in the present study. Of the 728 patients, seven had diabetes mellitus, and none had HIV infection or were undergoing hormone replacement therapy.

In addition, our study also showed that there were no significant differences in most behavioral factors between the two groups except for abortion and vaginal lavage. The risk of RVVC development appears to increase with an increase in the number of abortions. Patients with two or three abortions

are more likely to experience RVVC. However, we noticed that when the number of abortions was ≥ 4 , the odds ratio declined slightly with no statistically significant difference between the two groups. The limited sample size of this study may explain this finding. In the past, some studies conducted in China have revealed that repeat abortions increase the risk of VVC [23], but similar evidence is not readily available for RVVC. However, the reason why patients who have undergone repeat abortions are more likely to experience RVVC is still unknown. We suspect that repeat abortions are correlated with unprotected sex and multiple pregnancies, which are known risk factors for RVVC [24]. Pregnancy is associated with an increased vaginal colonization rate and stimulates the adherence of *Candida albicans* to vaginal epithelial cells *in vitro* [25]. Moreover, misoprostol, which is often used to induce abortion, is an endogenous suppressor of innate immunity [26]. It is not known whether the vaginal operative procedures or drugs involved in abortion can change the microenvironment of the vagina, and further research is required to clarify this issue. Moreover, we found that patients who practised vaginal lavage had a higher risk for RVVC. These findings support the results of previous work in which vaginal lavage was a risk factor for RVVC, but disagree with the results of other studies where no such relationship was found [27]. Because vaginal lavage alters the distribution of Lactobacillus species, which are effective for the treatment of RVVC [28], clinicians should advise patients with VVC to avoid vaginal lavage.

One of the most important aspects of VVC treatment is health education for patients. In our study, most behavioral habits were not risk factors for RVVC. In addition, most patients have healthy lifestyles. Many likely wear cotton underwear, change their underwear every day, wash their underwear separately, and shower daily. The results of our study could not confirm the results of previous studies that identified risk factors such as wearing nylon or synthetic underwear [27] and using panty liners. However, the results of a previous study support our finding that wearing panty liners does not promote VVC [29]. The results of the present study indicate that showering twice a day may protect women against recurrence of VVC. While some people living in tropical coastal areas bathe twice a day, this is difficult to accomplish for most people in these areas. The external vulva represents a site of *C. albicans* persistence and a source of endogenous re-infection in patients with RVVC [29]. Taken together, these findings suggest that good hygiene is conducive to reducing the recurrence of VVC.

As has been stated, we conclude that previous antibiotic treatment was the most important host factor in the pathogenesis of recurrent vulvovaginal candidiasis in tropical Sanya, China. Most behavioral factors have little effect on the recurrence of VVC, except for repeated abortions and vaginal lavage. In addition, more than two showers per day may have a protective effect on recurrent infections. Therefore, we may pay attention to antibiotic abuse in the future treatment

to prevent VVC recurrence. In addition, maintaining good hygiene practices is also a necessary means of preventing VVC.

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References

- Sobel JD. Vulvovaginal candidosis. *Lancet*. 2007; 369: 1961-1971. [PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17560449](https://www.ncbi.nlm.nih.gov/pubmed/17560449)
- Aballéa S, Guelfucci F, Wagner J, Khemiri A, Dietz J-P, et al. Subjective health status and health-related quality of life among women with Recurrent Vulvovaginal Candidosis (RVVC) in Europe and the USA. *Health Qual Life Outcomes*. 2013; 11: 169. [PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24119427](https://www.ncbi.nlm.nih.gov/pubmed/24119427)
- Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016; 62: e1-50. [PubMed: https://www.ncbi.nlm.nih.gov/pubmed/26679628](https://www.ncbi.nlm.nih.gov/pubmed/26679628)
- Sobel JD, Wiesenfeld HC, Martens M, Danna P, Hooton TM, et al. Maintenance Fluconazole Therapy for Recurrent Vulvovaginal Candidiasis. *N Engl J Med*. 2004; 351: 876-883. [PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15329425](https://www.ncbi.nlm.nih.gov/pubmed/15329425)
- Mending W, Seebacher C. Working Group for Infections and Infectimmunology of the German Society for Gynecology and Obstetrics; German Speaking Mycological Society; German Dermatological Society. Guideline vulvovaginal candidosis: guideline of the German Dermatological Society, the German Speaking Mycological Society and the Working Group for Infections and Infectimmunology of the German Society for Gynecology And Obstetrics. *Mycoses*. 2003; 46: 365-369. [PubMed: https://www.ncbi.nlm.nih.gov/pubmed/14622383](https://www.ncbi.nlm.nih.gov/pubmed/14622383)
- Bolouri F, Moghadami Tabrizi N, Davari Tanha F, Niroomand N, Azmoodeh A, et al. Effectiveness of Fluconazole for Suppressive Maintenance Therapy in Patients with RVVC: a Randomized Placebo-Controlled Study. *Iran J Pharm Res*. 2009; 8: 307-313.
- Sobel JD. Recurrent vulvovaginal candidiasis. *Am J Obstet Gynecol*. 2016; 214: 15-21. [PubMed: https://www.ncbi.nlm.nih.gov/pubmed/26164695](https://www.ncbi.nlm.nih.gov/pubmed/26164695)
- Sobel JD. Candida vulvovaginitis. *Clin Obstet Gynecol*. 1993; 36: 153-165. [PubMed: https://www.ncbi.nlm.nih.gov/pubmed/8435940](https://www.ncbi.nlm.nih.gov/pubmed/8435940)
- Powell K. Vaginal thrush: quality of life and treatments. *Br J Nurs*. 2010; 19: 1106-1111. [PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20871514](https://www.ncbi.nlm.nih.gov/pubmed/20871514)
- Sinkó J, Sulyok M, Denning DW. Burden of serious fungal diseases in Hungary. *Mycoses*. 2015; 58: 29-33. [PubMed: https://www.ncbi.nlm.nih.gov/pubmed/26449504](https://www.ncbi.nlm.nih.gov/pubmed/26449504)
- Corzo-León DE, Armstrong-James D, Denning DW. Burden of serious fungal infections in Mexico. *Mycoses* 2015; 58: 34-44. [PubMed: https://www.ncbi.nlm.nih.gov/pubmed/26449505](https://www.ncbi.nlm.nih.gov/pubmed/26449505)
- Kennedy MA, Sobel JD. Vulvovaginal Candidiasis Caused by Non-albicans Candida Species: New Insights. *Curr Infect Dis Rep*. 2010; 12: 465-470. [PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21308556](https://www.ncbi.nlm.nih.gov/pubmed/21308556)
- Foxman B, Muraglia R, Dietz JP, Sobel JD, Wagner J. Prevalence of recurrent vulvovaginal candidiasis In 5 European countries and the United States: results from an internet panel survey. *J Low Genit Tract Dis*. 2013; 17: 340-345. [PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23486072](https://www.ncbi.nlm.nih.gov/pubmed/23486072)
- Gross N, Arias M, Moraga M, Baddasarow YC. Species distribution and susceptibility to azoles of vaginal yeasts isolated prostitutes. *Infect Dis Obstet Gynecol*. 2007; 2007: 82412. [PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18273407](https://www.ncbi.nlm.nih.gov/pubmed/18273407)
- Mahmoudi Rad M, Zafarghandi S, Abbasabadi B, Tavallaee M. The epidemiology of Candida species associated with vulvovaginal candidiasis in an Iranian patient population. *Eur J Obstet Gynecol Reprod Biol*. 2011; 155: 199-203. [PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21194828](https://www.ncbi.nlm.nih.gov/pubmed/21194828)
- Liu XP, Fan SR, Peng YT, Zhang HP. Species distribution and susceptibility of Candida isolates from patient with vulvovaginal candidiasis in Southern China from 2003 to 2012. *J Mycol Med*. 2014; 24: 106-111. [PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24746725](https://www.ncbi.nlm.nih.gov/pubmed/24746725)
- Xu J, Schwartz K, Bartoces M, Monsur J, Severson RK, et al. Effect of Antibiotics on Vulvovaginal Candidiasis: A MetroNet Study. *J Am Board Fam Med*. 2008; 21: 261-268. [PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18612052](https://www.ncbi.nlm.nih.gov/pubmed/18612052)
- Li Y, Xu J, Wang F, Wang B, Lu Z. Overprescribing In China, Driven By Financial Incentives, Results In Very High Use Of Antibiotics, Injections, And Corticosteroids. *Health Aff*. 2012; 31: 1075-1082. [PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22566449](https://www.ncbi.nlm.nih.gov/pubmed/22566449)
- Patel DA, Brenda G, Sobel JD, Debbie L, Paul N, et al. Risk factors for recurrent vulvovaginal candidiasis in women receiving maintenance antifungal therapy: results of a prospective cohort study. *Am J Obstet Gynecol*. 2004; 190: 644-653. [PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15041994](https://www.ncbi.nlm.nih.gov/pubmed/15041994)
- Janković S, Bojović D, Vukadinović D, Daglar E, Janković M, et al. Risk factors for recurrent vulvovaginal candidiasis. *Vojnosanit Pregl*. 2010; 67: 819-824. [PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21061843](https://www.ncbi.nlm.nih.gov/pubmed/21061843)
- Amouri I, Sellami H, Borji N, Abbes S, Sellami A, et al. Epidemiological survey of vulvovaginal candidosis in Sfax, Tunisia. *Mycoses*. 2011; 54: e499-e505. [PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21039942](https://www.ncbi.nlm.nih.gov/pubmed/21039942)
- Gonçalves B, Ferreira C, Alves CT, Henriques M, Azeredo J, et al. Vulvovaginal candidiasis: Epidemiology, microbiology and risk factors. *Crit Rev Microbiol*. 2016; 42: 905-927. [PubMed: https://www.ncbi.nlm.nih.gov/pubmed/26690853](https://www.ncbi.nlm.nih.gov/pubmed/26690853)
- Fang X, Zhou Y, Yang Y, Diao Y, Li H. Prevalence and risk factors of trichomoniasis, bacterial vaginosis, and candidiasis for married women of child-bearing age in rural shandong. *Jpn J Infect Dis*. 2007; 60: 257-261. [PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17881863](https://www.ncbi.nlm.nih.gov/pubmed/17881863)
- Hellberg D, Zdolsek B, Nilsson S, Mårdh PA. Sexual behavior of women with repeated episodes of vulvovaginal candidiasis. *Eur J Epidemiol*. 1995; 11: 575-579. [PubMed: https://www.ncbi.nlm.nih.gov/pubmed/8549733](https://www.ncbi.nlm.nih.gov/pubmed/8549733)
- Segal E, Soroka A, Schechter A. Correlative relationship between adherence of *Candida albicans* to human vaginal epithelial cells in vitro and candidal vaginitis. *Sabouraudia*. 1984; 22: 191-200. [PubMed: https://www.ncbi.nlm.nih.gov/pubmed/6379915](https://www.ncbi.nlm.nih.gov/pubmed/6379915)
- Aronoff DM, Hao Y, Chung J, Coleman N, Lewis C, et al. Misoprostol impairs female reproductive tract innate immunity against *Clostridium sordellii*. *J Immunol*. 2008; 180: 8222-8230. [PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18523288](https://www.ncbi.nlm.nih.gov/pubmed/18523288)



27. Ekpenyong CE, Inyang-etoh EC, Etebong EO, Akpan UP, Ibu JO, et al. Recurrent vulvovaginal candidosis among young women in south eastern Nigeria: the role of lifestyle and health-care practices. *Int J STD AIDS*. 2012; 23: 704-709.
PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/23104744>
28. Palacios S, Espadaler J, Fernández-Moya JM, Prieto C, Salas N. Is it possible to prevent recurrent vulvovaginitis? The role of *Lactobacillus plantarum* I1001 (CECT7504). *Eur J Clin Microbiol Infect Dis*. 2016; 36: 1701-1708.
PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/27393491>
29. Farage M, Bramante M, Otaka Y, Sobel J. Do panty liners promote vulvovaginal candidiasis or urinary tract infections: A review of the scientific evidence. *Eur J Obstet Gynecol Reprod Biol*. 2007; 132: 8-19.
PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/17204360>