

# Probiotics and Treatment of Vulvovaginal Candidiasis



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## Abstract

**Background:** Genital infections are among the most common diseases for which women refer to gynecologists. Vulvovaginal candidiasis is the second most common infection among women.

**Objective:** A few studies have been conducted on new therapeutic regimens improving the effectiveness of current medications; accordingly, the present study was conducted to compare the effectiveness of clotrimazole with clotrimazole plus probiotics in the treatment of vulvovaginal candidiasis.

**Materials and Methods:** The present double-blind clinical trial was conducted on 80 women admitted to Shohada hospital in Tehran in 2014. The participants were randomly divided into 2 groups of clotrimazole and clotrimazole plus probiotics. The collected data included the participants' sociodemographic information and their medical records along with their symptoms and laboratory results before and after the treatment. Finally, the collected data were analyzed using chi-square test, *t* test, McNemar test and Fisher's exact test.

**Results:** The results showed that both treatments (i.e. clotrimazole and clotrimazole plus probiotics) are equally effective in the treatment of vulvovaginal candidiasis ( $P=0.499$ ).

**Conclusion:** The results of the present study indicated that supplementing clotrimazole with probiotics results in similar effects compared to administering clotrimazole alone in the treatment of vulvovaginal candidiasis.

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## Background

Vaginitis is the most common gynecologic problem for which women seek medical help.<sup>1,2</sup> Vulvovaginal candidiasis is the second most common infection among women. About 75% of women experience vulvovaginal candidiasis at least once during their lives; almost 45% experience vulvovaginal candidiasis more than 2 times per year; and 5% suffer from recurrent vulvovaginal candidiasis.<sup>3</sup>

Factors such as antibiotic therapy, estrogen therapy, diabetes, pregnancy, tight underwear, prior history of genital infections, contraception, use of oral contraceptives, consumption of corticosteroids or immunosuppressive drugs and frequent intercourse changing vaginal flora can increase the risk of vulvovaginal candidiasis.<sup>2,4,5</sup>

It is said that *Candida albicans* is responsible for 80% to 90% of cases of vulvovaginal candidiasis.<sup>5,6</sup> Some researchers point to an increase in the incidence of other species of *Candida*, possibly caused by an excessive use of over-the-counter medicines andazole drugs or temporary use of antifungal medications.<sup>7</sup>

Although the pathogenesis of vulvovaginal candidiasis

is still controversial, it seems that the balance among the microorganisms in the vagina is disturbed and it can facilitate overgrowth of *Candida*.<sup>2,8</sup>

Vulvovaginal candidiasis not only causes physical problems such as vulvar pruritus, vaginal discharge, burning urination, dyspareunia, irritation and erythema, and a waste of time and money, but also it causes psychological problems, especially in chronic or untreated forms. Furthermore, vulvovaginal candidiasis can negatively affect one's sexual orientation and thereby disrupts one's life.<sup>6,9,10</sup>

Several local and oral drugs are currently available for the treatment of vulvovaginal candidiasis; however, none of them has offered a major advance. Short-course formulations effectively treat vulvovaginal candidiasis in more than 90% of the cases. Clotrimazole is commonly considered as first-line treatment for vulvovaginal candidiasis.<sup>7</sup> However, recurrence of vulvovaginal candidiasis has been observed in many cases treated by clotrimazole alone and considering that vulvovaginal candidiasis affects vaginal flora, attempts have been made to prevent infection using lactobacilli (probiotics).<sup>10,11</sup>

As part of the overall human flora, probiotics are living, harmless, nonpathogenic and non-toxic bacteria; they can survive when passing the gastrointestinal tract and apply their beneficial effects.<sup>12</sup> The 2 major groups of probiotic microorganisms are lactobacilli and bifidobacteria.<sup>13,14</sup> Lactobacilli are the primary colonizing bacteria of the vaginal tract. It is believed that they can inhibit the growth of pathogenic microorganisms and play important roles in preventing genital infections and improving the genital microflora defense against bacterial infections.<sup>15</sup> For instance, secretion of organic acids and production of hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) by normal flora bacteria living in the female reproductive tract, such as *Lactobacillus* spp., inhibit the growth of *C. albicans*.<sup>16</sup> In studies on the effectiveness of probiotics in the treatment of vaginal infections, researchers have generally focused on bacterial vaginosis and only a few have examined vulvovaginal candidiasis. Some of these studies have shown the effectiveness of probiotic lactobacilli in the treatment of vulvovaginal candidiasis,<sup>10,15</sup> while others have not confirmed it. Accordingly, the effectiveness of probiotics in the treatment of vulvovaginal candidiasis is still controversial.<sup>4,17-19</sup>

Given the above-mentioned issues, the relatively high incidence of vulvovaginal candidiasis in Iran, multiple complications associated with chemical drugs for vulvovaginal candidiasis treatment and the resistance of microorganisms to these drugs, the need for improving the effectiveness of existing treatments and the lack of consensus about the value of probiotics in the treatment of vulvovaginal candidiasis, the present study was conducted to compare the effectiveness of clotrimazole vaginal cream with clotrimazole vaginal cream plus vaginal probiotic capsules in the treatment of vulvovaginal candidiasis.

## Materials and Methods

The present double-blind clinical trial was conducted on 15 to 45-year-old women admitted to Shohada hospital with vulvovaginitis. The participants were randomly divided into 2 groups of clotrimazole and clotrimazole plus probiotics (40 patients in each). The exclusion criteria included having sexual partner(s) other than husband, being pregnant, being a lactating mother, using any type of vaginal infection medications/antibiotics/debilitating drugs, having intercourse or vaginal douching over the last 24 hours, having intercourse without condom during the treatment, having other types of vaginal infection or diagnosed illness (e.g. diabetes) during the treatment, becoming pregnant or having a period during the treatment and having allergic reactions to either clotrimazole or probiotics.

In this study, a checklist to gather patients' demographic and medical information and another one to collect data regarding signs and symptoms of vulvovaginal candidiasis (i.e. abnormal vaginal discharge, vulvar pruritus, burning urination, dyspareunia, painful urination, inflammation

and redness of the vulva, vulvar edema and vaginal pH) were used.

In the lithotomy position and after inserting a sterile speculum with no lubrication, the vagina and cervix were examined for inflammation and possible abnormalities in color, consistency and smell of the discharge among all patients admitted to Women's Clinic of Shohada hospital. The samples were also examined for evidence of vaginal trichomoniasis, bacterial vaginosis and candidiasis. Vulvovaginal candidiasis was diagnosed with microscopic examination of vaginal secretions in 1 drop of 10% potassium hydroxide solution to see the presence of *C. albicans* hyphae bundles and amine odor. Key cells and *Trichomonas vaginalis* were examined microscopically in 1-2 drops of normal saline for trichomoniasis. Patients with candidiasis were randomly divided into the mentioned 2 groups after explaining the objectives of the study and obtaining written informed consent. Each participant received instructions for taking her medications. A vaginal capsule containing *Lactobacillus casei* and *Lactobacillus rhamnosus* was used as a probiotic regime once a day for over 14 days and clotrimazole vaginal cream as a routine drug regime for both groups was administered. The participants were asked to refer back to the clinic 3 to 7 days after the end of their treatment. Then, their clinical symptoms and laboratory results were re-examined. The treatment would be considered successful if the signs and symptoms of the diseases disappeared 3 to 7 days after the end of the treatment. Finally, using the SPSS software package version 17.0, the collected data were analyzed through statistical procedures of chi-square test, *t* test, McNemar test and Fisher exact test at statistical significance level of 0.05.

## Results

The results of *t* test indicated no significant difference in sociodemographic factors between the 2 groups (Table 1). Similarly, the results of chi-square test showed no significant difference between the 2 groups in terms of education level, occupation, menstrual status (regular vs. irregular) and the type of contraceptive.

Within-group and between-group comparison of patients' complaints, symptoms and vaginal pH are respectively presented in Tables 2 and 3.

The results of chi-square test did not show any significant difference in burning urination, dyspareunia or painful urination between the 2 groups; however, a significant difference was observed in inflammation and redness of the vulva ( $P=0.039$ ).

As shown in Table 4, chi-square test results did not indicate any significant difference between the 2 groups in terms of response to treatment ( $P=0.499$ ).

## Discussion and Conclusion

In this study, the most common complaints in both groups were pruritus and abnormal vaginal discharge

**Table 1.** Comparison of Sociodemographic Factors Between the 2 Groups

Variables	Clotrimazole Mean (SD)	Clotrimazole & Probiotics Mean (SD)	P Value
Age (y)	33.40 (6.05)	33.15 (6.19)	0.856
Age of marriage (y)	21.68 (4.08)	22.53 (4.09)	0.355
Length of marriage (ye)	11.65 (6.66)	10.50 (6.76)	0.446
Age at first pregnancy (y)	23.44 (4.11)	24.17 (3.89)	0.447
Gravidity (number of pregnancy)	2.47 (1.34)	2.58 (1.75)	0.432
Parity (number of delivery)	1.93 (1.18)	1.93 (1.23)	0.905
Cesarean delivery	0.48 (0.68)	0.48 (0.75)	0.811
Natural childbirth	1.45 (1.28)	1.45 (1.30)	0.980
Number of miscarriage (s)	0.57 (0.71)	0.55 (0.85)	0.603
Number of abortion (s)	0.23 (0.42)	0.10 (0.38)	0.703

**Table 2.** Within-Group Comparison of Complaints, Symptoms and Vaginal pH

Complaints	Groups									
	Clotrimazole					Clotrimazole & Probiotics				
	Before the treatment		After the treatment		P Value	Before the treatment		After the treatment		P Value
	No.	%	No.	%		No.	%	No.	%	
Vaginal discharge	40	100	16	40	-	35	87.5	17	42.5	<0.0001
Vulvar pruritus	37	92.5	12	30	<0.0001	38	95	13	32.5	<0.0001
Burning urination	21	52.5	3	7.5	<0.0001	5	37.5	4	10	0.001
Dyspareunia	13	32.5	3	7.5	0.006	17	42.5	2	5	<0.0001
Painful urination	8	20	3	7.5	0.180	8	20.5	2	5.1	0.070
Inflammation and redness of the vulva	38	95	9	22.5	<0.0001	27	67.5	9	22.5	<0.0001
Vulvar edema	6	15	2	5	0.219	13	32.5	0	0	-
pH <4.5	37	92.5	38	95	1.000	26	65	35	87.5	0.022

**Table 3.** Between-Group Comparison of Complaints, Symptoms and Vaginal pH

Complaints	Groups	Improved		Unchanged		Worsened		P Value
		No.	%	No.	%	No.	%	
Vaginal discharge	Clotrimazole	24	60	16	40	-	-	0.179
	Clotrimazole & Probiotics	18	45	22	55	-	-	
Vulvar pruritus	Clotrimazole	25	62.5	15	37.5	-	-	1.000
	Clotrimazole & Probiotics	25	62.5	15	37.5	-	-	
Burning urination	Clotrimazole	18	45	22	55	-	-	0.104
	Clotrimazole & Probiotics	11	27.5	29	72.5	-	-	
Dyspareunia	Clotrimazole	11	27.5	28	70	1	2.5	0.493
	Clotrimazole & Probiotics	16	40	23	57.5	1	2.5	
Painful urination	Clotrimazole	7	17.5	21	77.5	2	5	0.840
	Clotrimazole & Probiotics	14	17.5	63	78.5	3	3.8	
Inflammation and redness of the vulva	Clotrimazole	29	72.5	11	27.5	-	-	0.039
	Clotrimazole & Probiotics	19	47.5	20	50	1	2.5	
Vulvar edema	Clotrimazole	5	12.5	34	85	1	2.5	0.059
	Clotrimazole & Probiotics	13	32.5	27	67.5	-	-	
pH <4.5	Clotrimazole	2	5	35	87.5	3	7.5	0.059
	Clotrimazole & Probiotics	2	5	27	67.5	11	27.5	

and inflammation and redness of the vulva were the most common symptoms of vulvovaginal candidiasis. Similarly, Ramezani Tehrani et al<sup>20</sup> showed that abnormal

vaginal discharge was the main symptom of vulvovaginal candidiasis. The results of this study showed that 37 patients (92.5%) in the clotrimazole group and 26 patients

**Table 4.** The Rates of Positive/Negative Responses to the Treatment Methods

Treatment outcome	Groups		Total No. (%)	P Value
	Clotrimazole No. (%)	Clotrimazole & Probiotics No. (%)		
Successful	21 (52.5)	24 (60)	45 (56.3)	0.499
Failed	19 (47.5)	16 (40)	35 (43.8)	0.499

(65%) in the clotrimazole plus probiotics group had pH <4.5 before the treatment. Speroff and Fritz<sup>21</sup> believed that *Candida* infection normally occurs in the postmenstrual period because the elevated pH during menstruation makes it possible for *Candida* organisms to colonize. Runeman et al<sup>22</sup> stated that vaginal pH in healthy women and in women with vulvovaginal candidiasis is about 4.5, which is consistent with results of the present study.

The results also indicated that symptoms of abnormal vaginal discharge, burning urination and inflammation and redness of the vulva significantly improved after the treatment in both groups. According to the results of this study, complementary treatment of vulvovaginal candidiasis with *Lactobacillus* species acted the same as its conventional treatment with clotrimazole alone. Accordingly, both treatments (i.e. clotrimazole and clotrimazole + probiotics) relieved symptoms of vulvovaginal candidiasis similarly, except for vulvar inflammation and redness of the vulva.

In a study by Martinez et al,<sup>10</sup> 52 patients (89.7%) in the fluconazole plus probiotics group and 45 patients (61.5%) in the fluconazole plus placebo group positively responded to their treatments, indicating the effectiveness of probiotics in the treatment of infection. They stated that all patients (n=55) had positive cultures for *Candida* before the treatment and only 3 patients in the fluconazole plus probiotics group (10.3%) and 10 patients in the fluconazole plus placebo group (38.5%) had positive cultures for *Candida* after the treatment ( $P=0.01$ ). They also explained that all patients (n=55) had at least one of the symptoms of abnormal vaginal discharge, pruritus, burning urination or dyspareunia before the treatment and only 3 patients in the fluconazole plus probiotics group (10.3%) and 9 patients in the fluconazole plus placebo group (34.6%) had at least one of the mentioned symptoms after the treatment ( $P=0.03$ ). Tafazzoli Harandi<sup>12</sup> compared the effectiveness of metronidazole with metronidazole plus probiotics in the treatment of vulvovaginal candidiasis and found that the application of metronidazole plus probiotics is more effective ( $P<0.05$ ). He also reported no statistically significant difference between the 2 groups in terms of abnormal vaginal discharge, smelly vaginal discharge or vulvar pruritus; however, a clear tendency towards significance was observed in burning urination ( $P=0.06$ ).

In line with the results of this study, Martinez et al<sup>10</sup> reported that only 2 patients (6.9%) in the fluconazole plus probiotics group and 1 patient (3.8%) in the fluconazole

plus placebo group had pH >4.5 after the treatment.

In a double-blind clinical trial, Nouraei et al<sup>23</sup> compared the effectiveness of fluconazole with the fluconazole plus oral protexin in the treatment of vulvovaginal candidiasis. According to their findings, both methods were equally effective in the treatment of vulvovaginal candidiasis. They reported that the symptom of burning urination significantly changed after the treatment in the fluconazole plus oral protexin group ( $P=0.02$ ). Moreover, the rate of positive response to treatment ( $P=0.01$ ) and recovery period ( $P=0.04$ ) were significantly lower in the fluconazole plus oral protexin group and in a double-blind randomized clinical trial conducted on women aged 18 to 45 years in India, the addition of probiotics to the conventional antifungal therapy did not have any significant improvement.<sup>24</sup>

The differences between results of the present study and those of other similar studies can be attributed to the use of lactobacilli alone in some studies, different lactobacillus colonization, vaginal use of lactobacilli and the application of different drugs. Previous studies on the effectiveness of probiotics in the treatment of vulvovaginal candidiasis have shown relatively positive effects of these microorganisms on the rate of normal vagina flora regeneration by lactobacilli. It must be noted that these positive effects are not unlikely, given the many proposed mechanisms of probiotics. Given the fact that vulvovaginal candidiasis is the second most common vaginal infection after bacterial vaginosis and due to multiple complications associated with chemical drugs for vulvovaginal candidiasis treatment and the resistance of microorganisms to these drugs, there is a strong need for a complementary dietary regimen. The results of this study showed that both treatments (i.e. clotrimazole and clotrimazole plus probiotics) are equally effective in the treatment of vulvovaginal candidiasis. Therefore, future studies are required to confirm the effectiveness of probiotics in the treatment of vaginitis, especially *Candida* vaginitis.

#### Authors' Contributions

SS: designing, sampling, management, and supervision; MF: reading and arrangement the final manuscript; LA, MA: sampling; MA: management and providing advice.

#### Ethical Approval

This study was approved by the Ethical Committee of Shahid Beheshti Medical Science University.

**Conflict of Interest Disclosures**

The authors declare that they have no conflict of interests.

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