Original Article

Practices of Lebanese gynecologists regarding treatment of recurrent vulvovaginal candidiasis

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Abstract

Background: A review of the literature clearly indicates the absence of one set of guideline in the treatment of recurrent vulvovaginal candidiasis. In Lebanon, as physicians are trained in European or American schools of medicine, locally or abroad, they may be approaching the issue of recurrent vulvovaginal candidiasis using various methods. **Aims:** A national survey was conducted among Lebanese gynecologists to assess therapeutic protocols most commonly adopted to treat recurrent vulvovaginal candidiasis. **Material and Methods:** All obstetricians-gynecologists registered with the Order of Physicians were targeted. Bivariate analyses, comparing groups with specific prescription preferences, were tested using relevant statistical tests. All variables with significant bivariate associations with the outcomes were initially planned for a multivariate regression analysis to assess their interactive effects. **Results:** The study confirms that different approaches are used to treat recurrent vulvovaginal candidiasis. Most gynecologists (70%) recommended fluconazole 150 mg as first-line treatment. Fluconazole alone was significantly preferred by North American trained physicians, whereas European trained ones preferred to prescribe it in combination. However different dosage regimens were used with duration of treatment ranging from 2 to 4 weeks, with or without maintenance. **Conclusions:** The study revealed large diversity in prescription pattern, closely related to the specialization background of the physician. There is a need to generate evidence to establish national guidelines.

Keywords: Fluconazole, Recurrent vulvovaginal candidiasis, Treatment patterns.

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Introduction

Recurrent vulvovaginal candidiasis (RVVC) is a prevalent opportunistic mucosal infection. This condition affects a significant number of otherwise healthy women of childbearing age. Gynecologic infections may adversely affect quality of life by causing discomfort, inconvenience and sexual dysfunction [1]. Patients who have chronic vulvovaginitis should be thoroughly evaluated to determine the specific etiology and to initiate appropriate therapy. Induction therapy, followed by a maintenance regimen, has been reported as reducing the likelihood of relapse [2-4].

Candida albicans accounts for approximately 80-90% of all vulvovaginitis cases. An estimated 75% of women have at least one episode of vulvovaginal candidiasis (VVC) within their lifetime, with 40% to 45% having two or more episodes [5]. VVC is considered recurrent "when at least four specific episodes occur in one year or at least three episodes unrelated to antibiotic therapy occur within one

year" [4]. Recurrent VVC differs from persistent infection by the presence of a symptom-free interval. RVCC is estimated to affect 5% of women with an initial episode [4].

RVVC can be idiopathic or caused by several different mechanisms, including [6, 7]: 1) Treatment-resistant Candida species other than C. albicans; 2) Frequent antibiotic therapy; 3) Contraceptive practices: diaphragms, spermicides and intrauterine devices indirectly promote the persistence of an initial infection. Oral contraceptive pills (OCP) stimulate estrogen and progesterone receptors in Candida, thus promoting fungal proliferation; 4) Immuno-compromised status due to illness or systemic therapy with corticosteroids or similar drugs; 5) Sexual activity with infected partners; 6) Hyperglycemia in diabetes: hyperglycemia enhances the ability of C. albicans to bind to vaginal epithelial cells; and 7) Pregnancy. The frequency of these risk factors largely explains the relatively common recurrence of VVC in women who contract the disease for the first time.

RVVC is notoriously difficult to manage. Systematic reviews that strongly support a particular pharmacological method of conventional management of RVVC over another are absent from medical literature. A review of the literature clearly indicates the absence of one set of universal treatment guidelines worldwide. Fluconazole is the treatment of choice for VVC and RVVC for American specialists [2]. However, various protocols have been suggested in case of recurrence. Recurrence after a first treatment may be related to non-albicans Candida species in 10% to 20% of cases. Therefore, in the presence of recurrences, vaginal cultures should be obtained to confirm non-albicans species that are not as responsive to conventional therapies [6]. The non-albicans species include Candida tropicalis, Candida glabrata and Candida krusei.

In episodes where C. albicans is confirmed, the recurrence may still respond to topical applications of antifungal drugs such as clotrimazole 1% (7-14 days) or to a one-dose oral treatment of fluconazole (150 mg) [4, 8]. However, some experts recommend repeating the oral fluconazole treatment at a dose of 100 mg, 150 mg, or 200 mg per day orally every third day for a total of three doses (day 1, 4 and 7) [4]. Recent US practice guidelines recommend an induction therapy with 10-14 days of a topical or oral azole [2]. The recommended 6-month maintenance regimens [2, 4, 8] include: 1) fluconazole 100mg, 150 mg or 200 mg orally once weekly; or 2) clotrimazole 500 mg vaginal suppositories once weekly; or 3) topical clotrimazole 200 mg twice weekly. It was demonstrated that a maintenance therapy with fluconazole 150 mg weekly for 6 months controls symptomatic episodes in 90% of women, with one half of the patients having prolonged symptom relief [3].

Longer courses of maintenance therapy (e.g. 1 year) may be required to completely suppress the infection. The ReCiDiF trial [9] demonstrated the efficacy and safety of an individualized, degressive, prophylactic regimen. The regimen includes an induction dose of 600 mg fluconazole during the first week, followed by a maintenance therapy of 200 mg weekly for 2 months, followed by 200 mg biweekly for 4 months, and 200 mg monthly for 6 months, according to individual response to therapy. Of women who were cured successfully after the induction phase, 90% were disease-free after 6 months of maintenance therapy and 77% were disease-free after 1 year.

In Lebanon, physicians trained in different schools of medicine or in different countries may be approaching the treatment of RVVC using various methods. A national survey among Lebanese gynecologists was conducted to assess the magnitude of diversity in RVVC therapeutic protocols. Specifically the objectives of this baseline survey were: 1) To assess therapeutic preferences in drug products, dosages, and regimens; and 2) To analyze demographic and professional variables affecting preferences.

Materials and Methods

This study was submitted for ethical clearance to the Ethical Review Board of Hotel-Dieu de France (HDF) University Hospital in Beirut, Lebanon. There was no potential for harm to participants in this study. Data was handled in confidentiality. Participation remained totally voluntary.

Design and Target Population

An exhaustive cross-sectional survey of all registered gynecologists-obstetricians in Lebanon was conducted. The target population included all 869 physicians currently registered with the Lebanese Order of Physicians as "obstetricians and gynecologists" [10].

Exclusion criteria

Were excluded: retired physicians, those who were out of the country at the time of the survey, as well as those practicing only as obstetricians**.** Physicians who were not reachable for an appointment for the survey and those who refused to participate in the study were also excluded.

Study questionnaire

A standardized questionnaire on preferences of Lebanese gynecologists regarding common RVVC therapeutic practices was completed during pre-arranged face-to-face interviews at convenient times in physician's clinics. The questionnaire assessed also a variety of personal and professional factors which may independently affect diagnostic and therapeutic preferences and practices.

Statistics Analysis

All variables were presented according to their nature: in frequencies and percentages for categorical ones, and in means, standard deviations (SD) and intervals for continuous ones. Bivariate analyses, comparing groups with specific prescription preferences, were tested using relevant statistical tests. Associations with a p-value ≤ 0.05

were considered significant. All variables with significant bivariate associations with the outcomes were initially planned for a multivariate regression analysis to assess their interactive effects. Data were compiled and analyzed using SPSS 16 (SPSS Inc., Chicago, Illinois).

Results

Demographic and Professional Characteristics of Participating Gynecologists

Three hundred fifty nine practicing gynecologists from all parts of Lebanon filled the questionnaire (41% of the estimated target population). Sixty four percent were males. More than 50% of the physicians specialized in Europe (33.4% in Eastern Europe, 20.9 in Western Europe), about 25% in Lebanon, and less than 10% in North America or Arab countries. Participants had a mean age of 47 years and a mean professional experience of 16.5 years. The areas of practice and all other demographic details are presented in Table 1.

Table 1 Demographic and professional characteristics of participating gynecologists -Lebanon, 2010 (N= 359)

Variables	n (%)[a]	mean (SD) [interval]
Gender		
Males	222 (64.0)	
Females	125 (36.0)	
Age (in years)		47.1 (8.8) [46-48]
Region of Practice		
Beirut	89 (24.8)	
Suburbs	69 (24.8)	
Mount-Lebanon (minus suburbs)	40 (11.1)	
North-Lebanon	54 (15.0)	
South-Lebanon	74 (20.6)	
Bekaa	31 (8.6)	
Country of Specialization		
Lebanon	89 (24.8)	
Eastern Europe	120 (33.4)	
Western Europe	75 (20.9)	
Arab countries	17 (4.7)	
North America	21 (5.8)	
Unknown	37 (10.3)	
Years of Practice		16.5 (8.4) [15.9-17.5]

[a]Totals do not add up because of missing data

RVVC treatment patterns

Prescription patterns in the treatment of RVVC are reported in Table 2. Most gynecologists (70%) recommended fluconazole 150 mg capsules alone (32.3%) or in combination (37.8%) as first-line treatment. The duration of treatment ranged from 2 to 4 weeks, with or without maintenance. Fluconazole 100 mg was used in combination only by 3.3% of physicians. The lower dose of 50 mg was used alone or in combination in less than 5% of cases. Acetarsol in combination with other drugs was the second most mentioned drug (3.3%) in first-line treatment, after fluconazole. Other drugs were prescribed by less than 19% of the physicians at even lower rates. Of all participants, 53.2% provided information on their second-line treatment preferences. Of those, more than 60% included more than one drug in their prescriptions. The oral route was the route of choice for most physicians in first-line treatment (92%), whereas local administration was preferred in the second-line treatment. Local administration as ovules, creams and douches accounted for 86% of the mode of administration in second-line treatment (Table 3).

Table 2 Prescription patterns in the treatment of recurrent vulvo-vaginal candidiasis (Rvvc) (N= 359 gynecologists)

Patterns[a]	n (%)
First-Line Treatment	
Fluconazole 150 (caps) (n= 252; 70.1%)	
Alone	**116 (32.3)**
Once weekly for one month with maintenance	9 (2.5)
Once weekly; one month without maintenance	49 (13.6)
Once weekly; 3 weeks with maintenance	4 (1.1)
Once weekly; 3 weeks without maintenance	20 (5.5)
Once weekly; 2 weeks with maintenance	3 (0.8)
Once weekly; 2 weeks without maintenance	12 (3.3)
Other frequencies	19 (5.3)
Combined	**136 (37.8)**
Fluconazole 100 (caps) (n=12; 3.3%)	
Alone	**0 (0)**
Combined	**12 (3.3)**
Fluconazole 50 (caps) (n= 17; 4.6%)	
Alone	**7 (1.9)**
Once daily for 10 days	6 (1.6)
Other frequencies	1 (0.2)
Combined	**10 (2.7)**
Acetasol (n= 12; 3.3%)	
Alone	**0 (0)**
Combined	**12 (3.3)**
Other drugs	**66 (18.7)**
Second-Line Treatment	
One drug	123 (34.7)
More than one drug	224 (62.3)

[a]Totals do not add up because of missing data

Table 3 Preferences in modes of administration in the treatment of recurrent vulvo-vaginal candidiasis (rvvc) (N=359 gynecologists)

Mode of Administration	First Line	Second Line
N (%)[a]	**340**	**191**
Oral	313 (92.0)	26 (13.6)
Cream	6 (1.8)	52 (27.2)
Ovules	21 (6.2)	106 (55.5)
Douche	0 (0)	7 (3.7)

[a]Totals do not add up because of missing data

Factors associated with treatment patterns

Table 4 summarizes the prescription patterns in first line treatment of RVVC according to demographic and professional variables. The largest proportion (43.2%) of gynecologists irrespective of gender, age or years of practice recommend fluconazole 150 mg in combination therapy. Such a trend was observed in most areas throughout the country except in North Lebanon, where fluconozole was least prescribed alone or in combination

(p<0.01). In contrast, a larger proportion (66.2%) prescribed flucononazole in combination in South-Lebanon (p<0.01). Fluconazole alone was more frequently prescribed by gynecologists in Beirut (38.2%) and in North-Lebanon (35.2%) than nationally (26.7%). Diversity in prescription patterns was most marked in North-Lebanon (46.3%). Fluconazole 150 mg alone was prescribed mainly by physicians who specialized in North America (61.9%) and in Lebanon (32.6%). Physicians trained in Arab countries preferred to prescribe fuconazole 150mg in combination therapy (64.7%). There were no clear prescription patterns for Lebanese-trained physicians as Fluconazole 150 mg alone or in combination were similarly prescribed (32.6% and 38.2%) whereas other patterns were almost equally used (29.2%) (Table 4).

Table 4 Prescription patterns in first line treatment of recurrent vulvo-vaginal candidiasis (rvvc) by demographic and professional variables (N= 359 gynecologists)

	Fluconazole 150 alone	Fluconazole 150 combined	All other patterns	P value
N (%)[a]	**96 (26.7)**	**155 (43.2)**	**108 (30.1)**	---
Gender				0.49
Males	60 (27.0)	92 (41.4)	70 (31.3)	
Females	31 (24.8)	60 (48.0)	34 (27.2)	
Age (years, SD)	47.2 (10.3)	46.9 (8.2)	47.5 (8.5)	0.87
Region of Practice	34 (38.2)	35 (39.3)	20 (22.5)	0.01
Beirut	19 (27.5)	26 (37.7)	24 (34.8)	0.54
Suburbs	11 (27.5)	18 (45.0)	11 (27.5)	0.93
Mount-Lebanon (minus suburbs)	19 (35.2)	10 (18.5)	25 (46.3)	<0.01
North-Lebanon	5 (6.8)	49 (66.2)	20 (27.0)	<0.01
South-Lebanon	7 (22.6)	17 (54.8)	7 (22.6)	0.38
Bekaa				
Country of Specialization				
Lebanon	29 (32.6)	34 (38.2)	26 (29.2)	0.33
Eastern Europe	28 (23.3)	51 (42.5)	41 (34.2)	0.91
West Europe	17 (22.7)	37 (49.3)	21 (28.0)	0.46
Arab countries	2 (11.8)	11 (64.7)	4 (23.5)	0.16
North America	13 (61.9)	5 (23.8)	3 (14.3)	<0.01
Practice (years,SD)	16.4 (9.7)	16.4 (7.4)	16.9 (8.4)	0.87

[a]Totals do not add up because of missing data

Discussion

There are currently no standardized recommendations regarding the treatment of RVVC. Different medical associations/countries have adopted different protocols and an optimal therapy has not yet been established. This survey covered a large spectrum of gynecologists representing various areas of practice, training backgrounds and demographic characteristics. While participants represented less than half the target population, there are no reasons to believe that a major selection bias has occurred. In Lebanon, physicians remain on the records of the Order of Physicians even though they are retired or expatriated. These physicians account for most of the missing target.

The absence of universal recommendations is reflected in the large diversity of protocols used by Lebanese gynecologists who participated in this national survey. About 50% who were trained in Eastern and Western Europe tended to predominantly favor the use of fluconozole 150 mg in combination with other drugs to treat RVVC. Those educated in North America tended to significantly prefer fluconazole 150 mg used alone, while those trained in Arabic countries (mostly Syria) were even more likely to prescribe the combination than European-formed gynecologists. Regarding the 25% of gynecologists who specialized in Lebanon, results reveal intermediate prescription patterns, which reflect training in French or American schools of practices.

There were regional differences associated with different therapeutic preferences. However, the country of specialization often determines the region in which a gynecologist ends up practicing. Thus the prescription preferences by regions of practice often mirror the therapeutic preferences acquired during those years of training. For example, most physicians who specialized in Eastern Europe or in Arab countries are currently practicing in the Bekaa or in South Lebanon and tend to reflect the practices predominantly in their countries of specialization.

The first-line treatment of RVVC includes fluconazole 150 mg. Despite the predominant use of fluconazole 150 mg alone in the safe control of RVVC, a majority of physicians prefer to prescribe it in combination with other drugs. Such an approach may be justified by the fact that a long-term cure remains difficult to achieve. In the recently published updated recommendations [2], the Infectious Diseases Society of America recommends once weekly oral fluconazole at a dose of 150 mg for six months after initial control of the recurrent episode, specifying that this is the most convenient and well-tolerated regimen. Although there is supportive evidence on the efficacy of specific protocols with fluconazole 150 mg dose in induction and maintenance therapy, the drug was prescribed in Lebanon at different dosage regimens, with duration of treatment ranging from 2 to 4 weeks, with or without maintenance therapy. Fluconazole 150 mg dose was in fact mostly prescribed once weekly for one month without maintenance therapy.

The oral route of administration is recommended in the first line treatment. Because of liver toxicity with ketoconazole, widespread use of oral therapy occurred only after the approval of fluconazole, which for the most part has mild self-limited side effects of GI intolerance and headache. Topical therapy causes local burning in 5% to 10% of patients and tends to be messier [6]. In terms of efficacy in RVVC, to our knowledge no trial has compared the oral to the topical administration of antifungals. Most experts recommend oral fluconazole on a weekly basis as a first line treatment for induction therapy as well as for

maintenance therapy. Fluconazole maintains therapeutic concentrations in vaginal secretions for at least 72 hours after the ingestion of a single 150 mg tablet [11]. Side-effects of single-dose fluconazole (150 mg) tend to be mild and infrequent. However, fluconazole interacts with multiple drugs and potential for drug interactions should be assessed before prescribing the drug. Because fluconazole is a category C drug in pregnancy, most clinicians treat pregnant patients with topical therapy to limit the amount of drug exposure [6].

Conclusion

This national survey was conducted among gynecologists to assess the therapeutic protocols most commonly adopted by Lebanese gynecologists concerning RVVC. Surprisingly it clearly appears that there is a wide variety of protocols in such a small country as Lebanon, which in fact reflects the diversity of educational backgrounds of practicing physicians. This in turn reflects the lack of one set of universal treatment guidelines.

A clinical trial is currently being planned to compare the effectiveness and safety of most common protocols with a proposed standard, in order to generate data for evidence-based national guidelines in the treatment of RVVC.

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