Prognosis and Long-Term Outcome of Women With Idiopathic Recurrent Vulvovaginal Candidiasis Caused by *Candida albicans*

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Objectives: This study evaluated use of long-term fluconazole beyond an initial 6-month course of weekly fluconazole in premenopausal patients with idiopathic recurrent vulvovaginal candidiasis (RVVC) due to *Candida albicans*.

Materials and Methods: A retrospective chart review was performed of women seen in Wayne State University Vaginitis Clinic with culture-confirmed idiopathic RVVC due to *Candida albicans* during a 10-year period (January 2006 to December 2015). Only patients without risk factors for secondary VVC and who initiated a 6-month course of weekly fluconazole therapy were selected. Data included long-term use of fluconazole therapy, treatment efficacy, and development of fluconazole resistance. Questionnaires were mailed to evaluate patient's experience after fluconazole therapy.

Results: Of 883 patients with RVVC based on clinical records, 191 with culture positive idiopathic RVVC due to *C. albicans* were started on the maintenance fluconazole regimen, and 147 (77.0%) completed 6 months of therapy. Of these, 107 (72.8%) continued or received maintenance past 6 months. The most common reason for additional fluconazole therapy was culture-confirmed VVC recurrence (55.1%), unconfirmed but possible VVC recurrence (16.8%), and patient preference (10.3%). The mean duration of fluconazole maintenance was 35.7 (range = 7–288) months. Fluconazole resistance emerged in 7.5% completing 6-month therapy. Upon questionnaire follow-up, 93.6% of 51 respondents reported benefit during maintenance regimen; however, 80.9% described relapse after discontinuing weekly therapy.

Conclusions: Fluconazole suppression therapy was highly effective in preventing VVC symptoms but was rarely curative and VVC relapse occurred frequently after discontinuation of maintenance therapy. The development of drug resistance in *C. albicans* isolates after long-term fluconazole maintenance therapy although uncommon is a previously unrecognized complication.

Key Words: recurrent, vulvovaginal candidiasis, C. albicans, fluconazole, maintenance therapy, drug resistance

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Recurrent vulvovaginal candidiasis (RVVC) is a disorder characterized by 3 or more episodes of symptomatic vulvovaginal inflammation per year, most often caused by *Candida albicans* (CA).[1,2] Much reporting of infection is based on self-diagnosis and over-the-counter treatment, making it difficult to reliably quantify true recurrent disease.[1–3] The estimated lifetime prevalence of RVVC is approximately 9% of women in their reproductive years and is higher in African-American women and lowest in postmenopausal women or prepubertal girls.[3,4] Worldwide prevalence of RVVC affects an estimated 138 million women.[5]

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A large proportion of episodes of VVC occur in the presence of risk factors or trigger mechanisms that cause disruption of host vaginal microbiota or immune system.[1,6] Known risk factors include antibiotic use, recurrent bacterial vaginosis, immunosuppression, and diabetes mellitus. However, some women are affected by idiopathic disease or primary RVVC, with attacks developing in the absence of risk factors.[2] The pathogenesis of idiopathic RVVC is likely the consequence of host genetic predisposition reflecting an immunologic susceptibility located and expressed in the vaginal mucosa.[7–13] Recurrence is associated either with a persistent vaginal reservoir of the fungal pathogen that emerges to cause relapse or by reinfection with an identical strain.[2,14,15] Attacks generally decrease when estrogen diminishes during menopause; however, postmenopausal women on hormone replacement therapy frequently continue to have attacks, suggesting a strong hormonal contribution to recurrence.[2] Most cases caused by CA are sensitive to fluconazole.[2,16,17]

RVVC infection is difficult to treat. In our clinic, the recommended treatment involves an induction phase of 150-mg fluconazole for 3 doses, followed by a maintenance course of 150-mg fluconazole weekly for 6 months.[16,18] During this suppressive regimen, symptomatic episodes are rare; however, many women experience recurrence of symptomatic infection after treatment discontinuation.[16,19] Studies have shown that more than 50% of patients experience relapse within 6 months of completing maintenance therapy, and this rate continues to grow as time passes.[16] In clinical practice, patients frequently require and prefer such suppressive maintenance therapy for an unlimited prolonged period rather than treatment of frequent individual episodes. Data regarding outcome or prognosis past 1 year of fluconazole treatment are significantly lacking. Recently, Crouss et al.[17] studied the long-term outcome of women with RVVC and concluded that although RVVC can be controlled using maintenance fluconazole therapy, relapse of symptomatic VVC was extremely common and cure infrequent. In the study by Crouss et al.,[17] patients with both primary and secondary RVVC were included. However, in the present study, we included only women with idiopathic, or primary, RVVC and specifically VVC due to *C. albicans.*

MATERIALS AND METHODS

This study is a retrospective observational analysis of women with idiopathic RVVC treated at a specialty vaginitis clinic for a 10-year period from 2006 to 2015. All patients with a suspected diagnosis of recurrent Candida infection were identified from scheduling records at the Infectious Disease Vaginitis Clinic of Wayne State University in Detroit, Michigan. Patients were included if older than 18 years, premenopausal, and with history of at least 3 attacks per year for a minimum duration of 3 years. From an initial list of 883 patients, various exclusion criteria were applied to isolate only patients with confirmed culture-positive idiopathic CA infection (see Figure 1), resulting in a final study group of 191 patients. Patients with nonalbicans Candida infections (NAC), recurrent bacterial vaginosis in conjunction with CA, or those with mixed Candida infections (CA + NAC) were

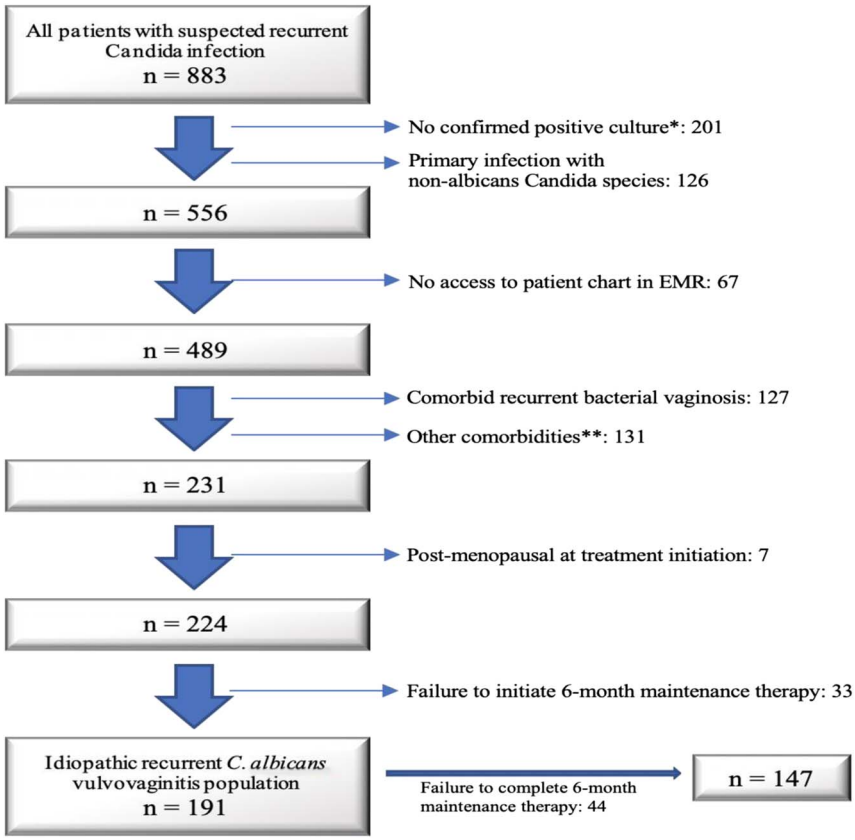

FIGURE 1. Exclusion criteria applied to initial list of patients with suspected diagnosis of RVVC identified using paper records from the vaginitis clinic. *Culture records obtained from Wayne State Research Laboratory—patients must have had at least one positive culture for CA before or during treatment. **Other comorbidities include known risk factors, as well as other disease processes that may alter the vulvovaginal environment leading to increased susceptibility to Candida infection. These include diabetes mellitus, atrophic vaginitis, desquamative inflammatory disease, herpes virus, vulvar eczema, psoriasis, lichen sclerosus, contact dermatitis, conditions requiring recurrent antibiotic use, and menopausal use of estrogen.

excluded. All patients in the final study group initiated the 6-month once-weekly 150-mg fluconazole maintenance dosing.

Data were collected for these 191 patients using the electronic medical record at the Infectious Disease Vaginitis Clinic. A retrospective chart review was then conducted, and an electronic record was established detailing patient demographics, course of RVVC infection, treatment regimens, response to treatments, and menopausal status.

The following variables were abstracted from chart review: date of first vaginitis clinic visit, age at first visit, race, body mass index (BMI) data, total duration of follow-up, perceived response to therapy after the initial 6-month maintenance phase, duration of continued fluconazole maintenance treatment after the initial 6-month course, current known or unknown RVVC status, resistance to fluconazole, additional therapy regimens, and use of oral contraceptives or intrauterine devices. Only patients who completed the 6-month maintenance course were included in the final data analysis set. Questionnaires were sent to patients to gather information regarding their long-term use of maintenance fluconazole, additional recent treatments, and current RVVC status (SDC1, http://links.lww.com/LGT/A130 and SDC2, http://links.lww.com/LGT/A131). A brief consent form was included in all letter packages along with a standardized questionnaire form and a deidentified return envelope. This study was approved by the Wayne State University Institutional Review Board (IRB ID: 044415MP2E). Susceptibility testing to all available antifungals including fluconazole was performed on those isolates of CA detected in women with refractory or breakthrough vulvovaginal symptoms while on fluconazole maintenance therapy.

RESULTS

During the decade, 2006–2015, 556 patients with culture positive RVVC were treated (see Figure 1). Two hundred sixty-five patients were excluded because of the presence of comorbid vulvovaginal pathology contributing to secondary RVVC (45.6%), almost half of whom had coexistent recurrent bacterial vaginosis. Thirty-three patients failed to initiate the maintenance phase of fluconazole therapy, leaving 191 patients with idiopathic RVVC due to CA who initiated 6-month maintenance therapy.

The average age of first visit to the vaginitis clinic for the sample group was 34.1 years (range = 17–55) (see Table 1). The mean duration of follow-up was 36 months (range = 0–127 months). The total group was represented by most white patients (63.9%), with the next largest racial group being African American (13.6%). In assessing BMI, 21 (14.2%) of 147 patients were identified as obese with a BMI ≥ 30, 22 (15%) were overweight with a BMI of 25 to 29, and 98 (66.7%) had a BMI of less than 25. Thirty-eight patients (29.5%) were using hormonal contraception in the form of oral, Nuva-Ring, patch, or Implanon at the time of initiation of therapy. Thirteen patients (6.8%) used Intrauterine devices (IUDs) (see Table 1).

TABLE 1. Demographics of Patients Identified With Idiopathic RVVC

Age at first vaginitis clinic visit, year	
Mean	34.1
Median	34
Range	17–55
Race	
White	112 (58.6%)
African American	26 (13.6%)
Asian	4 (2.1%)
Hispanic	2 (1.0%)
Middle Eastern	3 (1.6%)
Other	6 (3.1%)
Unknown	38 (19.9%)
BMI	
≥30	28 (14.7%)
25.0–29.9	29 (15.2%)
<25	120 (62.8%)
Unknown	14 (7.3%)
Contraceptive use	
None	121 (63.4%)
Non-IUD hormonal contraceptives (Nuva-Ring, patch, oral pills, or Implanon)	45 (23.5%)
Intrauterine device	
(IUD) total	13 (6.8%)
Mirena	7 (3.7%)
Paragard	1 (0.5%)
Unknown	5 (2.6%)

$N = 191$.

Forty-four patients (44, 23.0%) finished less than 6 months of once weekly maintenance fluconazole (due to self-discontinuation) or were lost to follow-up before the 6-month return visit, leaving 147 patients (77.0%) who completed 6 months of weekly fluconazole maintenance dosing. These 147 patients were used as the final sample population (see Figure 1). Of the 147 patients who completed maintenance therapy, 114 (77.6%) reported complete resolution of symptom and 30 (20.4%) reported improved or partial resolution of all symptoms while on therapy (see Table 2).

One hundred seven (72.8%) of the 147 patients who completed the initial 6 months of fluconazole maintenance therapy continued suppressive fluconazole weekly prophylaxis for greater than 6 months. Decision to extend treatment beyond 6 months, per electronic medical record documentation, was based on recurrence of symptoms after a period of discontinuation, incomplete resolution of symptoms, or for those who preferred to remain on treatment. Patients were not routinely screened for hepatic dysfunction. For these 107 patients, the mean duration of therapy was 35.7 months, with a range of 7 to 288 months of documented lifetime fluconazole maintenance treatment. In assessing reason for post–6-month continued therapy, the most common reason noted in the clinical document was culture-confirmed VVC recurrence (59, 55.1%), with secondary reasons being partial symptom resolution (18, 16.8%), patient preference in absence of clinical relapse (11, 10.3%), undocumented reason (6, 5.6%), drug resistance (6, 5.6%), poor adherence (5, 4.7%), and persistent culture positive (2, 1.9%).

All identified patients with idiopathic RVVC who began 6-month maintenance fluconazole after induction ($N = 191$) were sent letters for further follow-up. From extracted chart data, 26 patients (13.6%) were identified as still on maintenance fluconazole therapy (including 7 from 2006, 4 from 2007, and 3 from 2008) and 63 (33.0%) no longer received or were taking maintenance therapy.

Fifty-one questionnaires were completed and returned, comprising 26.7% of the total 191 sample group including 14 patients from the subgroup identified to still be using fluconazole weekly maintenance therapy. In total, the median current age for all patients identified by questionnaire was 43.2 years, and the average age of self-reported first vaginal candida infection was 22.5 years (median = 20 years). Respondents to the questionnaire ($n = 51$) included several patients still using maintenance fluconazole years after initial long term use. Of the 51 respondents, 92.2% reported benefit while using maintenance fluconazole, and 89.9% described frequent relapse of symptoms after discontinuation of suppression.

Of 191 patients with RVVC treated with induction and 6 months of weekly maintenance fluconazole, 13 patients (6.8%) developed breakthrough or refractory symptomatic episodes caused by CA resistant to fluconazole (Minimal Inhibitory Concentration >2 ug/mL) (see Table 3) One patient was identified by chart data to be still currently using high-dose (200 mg weekly) fluconazole maintenance, whereas the remainder used alternative, predominantly nonazole, regimens. Chart analyses reported average duration of past weekly fluconazole maintenance for the resistance group was 32.4 months with a median of 14 months and range of 2 to 204 months.

DISCUSSION

RVVC is anything but a mild nuisance malady, with worldwide distribution constituting an enormous human physical, emotional, and economic burden.[1,2,20] The introduction and wide acceptance of suppressive oral imidazole and triazole maintenance

TABLE 2. Outcomes After Standard Fluconazole Therapy for RVVC

Total RVVC patients	**191**	
No. completed standard 6-mo maintenance therapy	147	
Duration of maintenance therapy ($N = 191$), mo	Mean	27.6
	Median	16
Duration of continued therapy if requiring >6 mo of maintenance ($n = 107$), mo	Mean	35.7
	Median	21
	Range	7–288
Total duration of maintenance therapy	<6 mo	$n = 44$
	6	40
	7–12	27
	13–18	19
	19–24	17
	25–30	8
	31–36	9
	37–48	6
	49–60	6
	61–72	2
	73–84	2
	85–96	4
	97–108	3
	108+ mo	$n = 4$
RVVC status at follow-up appointment after completion of 6-mo maintenance ($n = 147$)	Asymptomatic	114 (7.6%)
	Partial symptom resolution	30 (20.4%)
	Undocumented	3 (2.0%)

TABLE 3. Fluconazole Resistance in Total Study Population

Prevalence	6.8%[3]
Mean of maintenance before diagnosis, mo	32.4
Range of maintenance therapy before diagnosis, mo	2–204

$N = 191$.

regimens have achieved a significant reduction in morbidity of this chronic problem using now generic, inexpensive, and predominantly safe antifungal agents. Several studies using largely similar regimens have confirmed the efficacy of this strategy to prevent and reduce the frequency of recurring episodes of symptomatic VVC.[16,19,21] However, long-term follow-up of women with RVVC after treatment cessation was lacking. In the original study using weekly fluconazole suppression by Sobel et al.[16] in 2004, a recurrent episode of symptomatic VVC was readily recognized in half the patients within 6 months of treatment cessation. Moreover, when women were followed for longer periods, an even higher rate of recurrence was revealed. Clinical experience, but unpublished data, indicates that maintenance fluconazole regimens were rarely curative but readily controlled or prevented troublesome recurrences of VVC as long as therapy was continued.[2] As evidenced in our current study, and that of Crouss et al.,[17] women experiencing RVVC overwhelmingly embraced the benefits of long-term suppressive therapy in preventing recurrences, despite awareness of the inability to cure this disease.

In the absence of long-term follow-up data, little was previously known regarding the prognosis of RVVC. Clearly, progress toward achieving cure might depend on the causation of RVVC, recognizing that although a genetic basis is likely operative in all susceptible women, attack triggering or precipitating factors are extremely variable.[8–13] In the study by Crouss et al.,[17] all women meeting the diagnosis of RVVC were included. Patients were not separated based upon risk factors. Women with comorbid vulvar diseases, for example. lichen sclerosus, possess an additional predisposing factor to Candida colonization by virtue of the chronic structural damage, combined with the additional contributory effect of topical corticosteroid therapy. Similarly, prognosis might be influenced by precipitating factors such as topical or systemic antibiotic therapy or diabetes mellitus. In an attempt to separate women with known contributory factors, we included only women with idiopathic RVVC devoid of associated systemic or local vulvar disease. One weakness of the current study, however, was inclusion of patients with an IUD in place, despite some prior studies indicating that IUD use may be a risk factor for candidiasis. Although both primary and secondary RVVC attacks frequently follow antibacterial therapy, most women with idiopathic primary RVVC experience recurrent episodes in the absence of recognizable predisposing factors.

In the present study, the outcome was identical to that of Crouss et al.[17] in that maintenance weekly fluconazole, even when prescribed effectively for 6 months, uncommonly achieved long-term cure. This indicates that the underlying genetically induced vaginal mucosal abnormality in women with idiopathic RVVC is rarely reversed by seemingly effective prolonged fluconazole therapy despite maintaining a persistent negative vaginal yeast culture status. In a questionnaire, patients affirmed the benefit of maintenance fluconazole. Until new understanding of pathogens emerges or new, more potent, antifungals become available, the current prophylactic antifungal regimens remain the optimal method of management.

The emergence of fluconazole resistance in this study, although it occurred in a few patients, is of clinical significance. Patients with RVVC who develop resistance to azoles are challenging to treat because the paucity of available nonazole agents makes selecting effective alternative regimens difficult.[22] When symptomatic infection recurred while on a regimen of maintenance fluconazole, resistance testing was performed and in vitro fluconazole resistance with Minimal Inhibitory Concentration of greater than 2 ug/mL was documented in 6.8% of patients (from the initial 191 who started treatment). In an earlier report, Marchaim et al.[23] described quantitative fluconazole exposure as predisposing to fluconazole resistance. In the current cohort, there was no consistent relationship between resistance and duration of fluconazole treatment. Resistance to fluconazole in this setting of CA isolates was frequently associated with in vitro resistance to the entire azole drug class (data not shown).

CONCLUSIONS

In this large, single-center retrospective cohort study, data emerged that women with idiopathic or primary RVVC continue to be at risk of symptomatic VVC recurrences for many years of reproductive ability. Although fluconazole prophylaxis contributes to symptom-free life, and although negative yeast culture status is achieved during therapy, cure is uncommon indicating that underlying host pathogenic factors remain active.

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