

Chronic vulvovaginal candidiasis: characteristics of women with *Candida albicans*, *C glabrata* and no candida

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Abstract

Introduction—Although as many as 5% of all women complain of chronic vulvovaginitis, little is known about these women. They may often be misdiagnosed and the role of vaginal yeast culture in diagnosing vulvovaginal candidiasis (VVC) among them has not been clearly defined.

Methods—To address these deficiencies, we tabulated initial diagnoses among new patients and conducted a medical record-based, unmatched case-control study among women reporting a history of chronic vulvovaginitis (four or more episodes in the past year) at a vulvovaginitis specialty clinic. Clinical presentation and medical history were compared for women who had a positive vaginal yeast culture for either *Candida albicans* or *C glabrata*, or who had a negative culture.

Results—One-third of the women had no apparent vulvovaginal disease at their initial visit. All women reported similar symptoms, except for an increased prevalence of painful sexual intercourse in women with *C albicans* (χ^2 $p = 0.014$ versus women with *C glabrata* and $p < 0.001$ versus women with no candida). Women with *C glabrata* were more likely to be non-white (χ^2 $p = 0.071$ compared with women with *C albicans*) and to report an underlying medical condition (χ^2 $p \leq 0.001$ versus both women with *C albicans* and women with no candida). Physical examination was normal only in women with no candida. *C albicans* cases were more likely to have positive potassium hydroxide microscopy (χ^2 $p = 0.016$) and a pH ≤ 4.5 (χ^2 $p = 0.011$) than were *C glabrata* cases.

Conclusions—These results suggest that reliance on symptoms and signs alone will result in significant misdiagnosis of chronic vulvovaginitis. Among women with VVC, subtle differences in clinical presentation do not reliably distinguish women with *C albicans* from those with *C glabrata*. Our study also indicates that vaginal yeast cultures, while not necessary for every patient, are valuable in confirming negative diagnoses, detecting microscopy false-negatives, and identifying non-*C albicans* isolates.

Keywords: candidiasis, vulvovaginal; diagnosis; recurrence

Introduction

Vulvovaginal candidiasis (VVC) is a syndrome characterised by vulvovaginal inflammation due to vaginal candida infection. Although precise incidence and prevalence estimates are unavailable, there is no question that VVC occurs frequently. In one family practice, 72% of 204 women aged 18 to 85 years with genitourinary symptoms reported at least one previous episode of VVC.¹ Among 373 population controls for a cancer study, 44.5% of women aged 20 to 49 years reported at least one episode of VVC in the past five years; of them, 44.6% had had five or more episodes.² These studies support the clinical impression that 75% of women will have at least one episode of VVC during their lives, with 40% to 50% experiencing second attacks and a small subset ($\leq 5\%$) experiencing chronic, recurring episodes.^{3,4} While women with chronic VVC constitute a small proportion of all women, they may experience symptomatic episodes as often as monthly and may consume disproportionate amounts of clinicians' time. The inability to cure these women quickly and completely is frustrating for both patients and clinicians.^{4,5}

Misdiagnosis of chronic vulvovaginitis due to inadequate patient evaluation may be common,⁵ as signs and symptoms alone are poor diagnostic tools. Diagnostic accuracy is improved with the use of conventional office tests such as saline and potassium hydroxide (KOH) microscopy.^{1,6-12} However, even if these tests are done properly they may fail to distinguish women with VVC from women with another or no vulvovaginal condition. Vaginal yeast culture may also be useful and is especially indicated in two groups of patients: (1) women with signs and symptoms suggestive of VVC but with negative microscopy and (2) women with positive microscopy who fail to respond to standard therapies who could be infected by non-*C albicans* species that may require more intensive or alternative therapeutic approaches.^{4,5,8,11,13-20}

In this medical record review study of women seen at a vulvovaginitis specialty clinic, we describe the initial diagnoses among women reporting a history of chronic vulvovaginitis and evaluate whether presenting signs, symptoms, office laboratory procedures, and medical history distinguish

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between groups identified by yeast culture. Specifically, we compare women reporting a history of chronic vulvovaginitis (four or more episodes in the past year) who received one of three initial diagnoses at the clinic: (1) acute VVC due to *C albicans*, (2) acute VVC due to *C glabrata* (formerly *Torulopsis glabrata*), and (3) women who appeared normal and had a negative vaginal culture for candida.

Methods

For our unmatched case-control study, we retrospectively reviewed the medical records of women who sought care from the head of a clinic specialising in the diagnosis and treatment of chronic vulvovaginal complaints. Women attending this clinic are referred by their clinician or refer themselves after multiple episodes of vulvovaginitis that do not respond to conventional therapies. Prior to their first visit women are asked to cease using all vaginal medications for approximately six weeks, to facilitate diagnosis and minimise any ambiguities in the physical examination due to hypersensitivity reactions to the medications.

Each woman's initial visit to the clinic includes collection of a detailed medical history and a thorough pelvic examination, including bimanual palpation, measurement of pH, amine testing, and microscopic examination with both 10% KOH and normal saline. A swab sample from the middle third of the vagina is placed on Sabouraud dextrose agar plates, which are incubated in CO₂. Identification of positive yeast cultures is based on germ-tube formation in human serum, chlamyospore production, and the results of carbohydrate assimilation profile tests (API-20C, Sherwood Medical, Plain-

view, NY). As indicated by examination, additional tests to exclude other vulvovaginal pathogens are conducted.

A case was defined as any symptomatic woman who received a diagnosis of vulvovaginitis on physical examination and had a positive vaginal yeast culture, with other causes of vulvovaginitis excluded. Cases were separated into two groups depending on the organism identified from the cultures, either *C albicans* or *C glabrata*. Controls consisted of women who had few or no presenting symptoms and were diagnosed as normal on physical examination after having no findings consistent with VVC or any other cause of vulvovaginitis. Controls also had negative microscopy and vaginal yeast cultures. Cases and controls all reported four or more episodes of vulvovaginitis in the past year. All 48 *C albicans* cases and a random sample of 64 controls who visited the clinic from January 1991 to March 1992 were included, while all 29 *Candida glabrata* cases identified since the start of the clinic in 1985 were used. No cases or controls were pregnant at the time of their initial visit.

Data were abstracted from a standard clinic intake form completed by the physician at each patient's initial visit. We collected information on demographic characteristics; menstrual, sexual, gynaecological and medical history; current complaints; physical examination results; and the diagnosis and treatment prescribed. Owing to the small sample size, we limited our statistical analysis to two-way χ^2 tests and Fisher exact tests when the χ^2 expected cell size criteria were violated; both were calculated using SAS.²¹ The study protocol was reviewed and approved by the Human Subjects Review Committee of the University of Michigan School of Public Health.

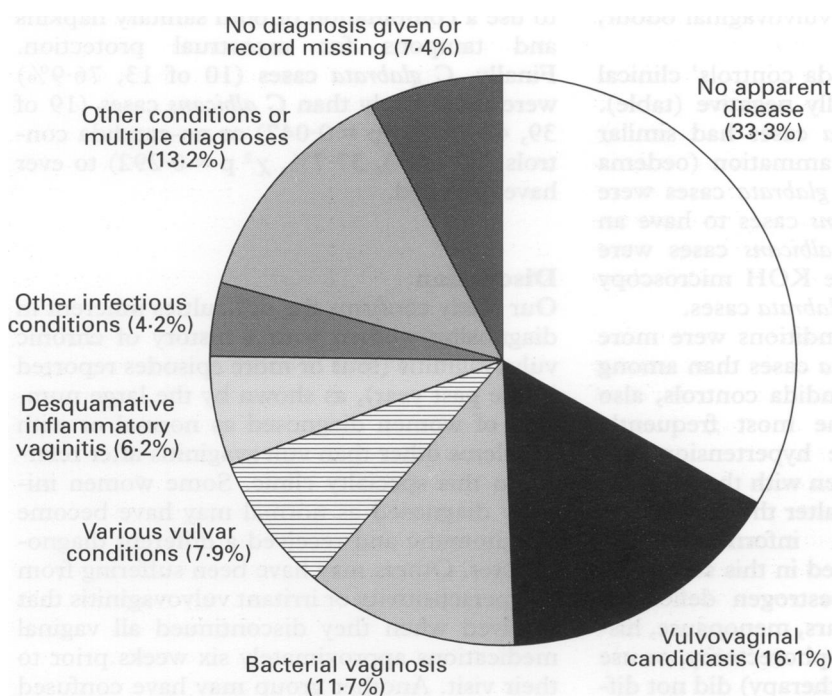
Results

INITIAL DIAGNOSES AMONG THE CLINIC POPULATION

The initial diagnoses of 403 new patients with chronic vulvovaginal complaints examined by any provider at the vulvovaginitis specialty clinic from January 1991 to March 1992 are shown in the fig. Although all women reported four or more episodes of vulvovaginitis in the past year, only about 30% were diagnosed with VVC or bacterial vaginosis, the most common forms of vulvovaginitis. One-third of women had no apparent vulvovaginal disease at their initial visit and were considered normal. The remaining women received many different diagnoses, including uncommon diseases such as desquamative inflammatory vaginitis and vulvar conditions like vulvar vestibulitis. The remaining results refer only to patients examined by the head of the clinic (JDS), who examines approximately two-thirds of all patients at their initial visit.

Case-control comparisons

C albicans cases (n = 48), *C glabrata* cases (n = 29) and no-candida controls (n = 64) were similar with respect to age, marital status



Distribution of Initial Diagnoses in a Vulvovaginitis Specialty Clinic (n = 403), January 1991 to March 1992

Characteristics of women reporting a history of chronic vulvovaginitis, by diagnosis at a vulvovaginitis specialty clinic

	<i>Candida albicans</i> vulvovaginal candidiasis (n = 48)		<i>Candida glabrata</i> vulvovaginal candidiasis (n = 29)		No apparent vulvovaginal disease and no candida (n = 64)		<i>Candida</i> <i>albicans</i> versus <i>Candida</i> <i>glabrata</i> p†	<i>Candida</i> <i>albicans</i> versus no candida p†	<i>Candida</i> <i>glabrata</i> versus no candida p†
	N	%*	N	%*	N	%*			
Demographic Characteristics:									
Age > 45 years	7	14.6	5	17.2	10	15.6	0.755	0.879	0.844
White race	34	75.6	10	52.6	43	69.4	0.071	0.481	0.180
Currently married	24	51.1	12	44.4	30	46.9	0.583	0.663	0.832
Employed	40	83.3	20	80.0	54	85.7	0.724	0.730	0.509
Symptoms:									
Duration ≥ 1 year	41	93.2	14	70.0	46	79.3	0.022‡	0.050	0.394
Discharge	42	93.3	23	88.5	55	96.5	0.662‡	0.652‡	0.175‡
Itch	38	88.4	23	85.2	39	72.2	0.726‡	0.051	0.194
Painful sexual intercourse	27	73.0	10	41.7	16	32.7	0.014	< 0.001	0.450
Clinical Presentation:									
Vulvar inflammation	31	66.0	11	57.9	5§	8.5§	0.538	< 0.001§	< 0.001‡§
Vaginal inflammation	29	64.4	12	57.1	0§	0.0§	0.569	< 0.001§	< 0.001§
pH > 4.5	8	17.8	10	47.6	6	9.8	0.011	0.233	< 0.001
KOH microscopy positive	34	70.8	12	42.9	0§	0.0§	0.016	< 0.001§	< 0.001§
Underlying medical condition	9	19.1	15	60.0	14	22.2	< 0.001	0.695	0.001‡

*Due to missing data, the denominator may be less than the total n given.

† χ^2 test, except as noted.

‡ χ^2 test expected cell size requirements violated, so Fisher exact test used.

§By definition, few or no controls had these characteristics, so these comparisons are somewhat artificial.

and employment (table). *C. glabrata* cases were somewhat less likely to be white than *C. albicans* cases and no-candida controls; the small sample size prevented this difference from achieving statistical significance at the $p = 0.05$ level.

Presenting symptoms differed only slightly between case and control groups (table). Painful sexual intercourse was much more common among *C. albicans* cases than among *C. glabrata* cases or no-candida controls. *C. albicans* cases were also more likely to have had recurring vulvovaginal complaints for a year or more. Discharge and itch were common among both case groups and no-candida controls, although *C. albicans* cases were more likely to report itching than controls. Although a high percentage of missing data ($\geq 40\%$) limited evaluation of other symptoms, both case groups and controls appeared to report similar levels of vulvovaginal odour, dryness, and burning.

By definition, no-candida controls' clinical presentation was essentially negative (table). *C. albicans* and *C. glabrata* cases had similar levels of vulvovaginal inflammation (oedema and/or erythema), but *C. glabrata* cases were more likely than *C. albicans* cases to have an elevated vaginal pH. *C. albicans* cases were much more likely to have KOH microscopy positive for yeast than *C. glabrata* cases.

Underlying medical conditions were more common among *C. glabrata* cases than among *C. albicans* cases or no-candida controls, also shown in the table. The most frequently reported conditions were hypertension and diabetes; removal of women with these conditions did not appreciably alter the results presented here. Although information on hormonal status was limited in this study, the occurrence of possible oestrogen deficiency (defined as age over 50 years, menopause, history of hysterectomy or oophorectomy, or use of oestrogen replacement therapy) did not differ between the case groups and controls. Both case groups and controls were similar

with regard to their history of sexually transmitted diseases, obstetrical-gynaecological procedures (including surgery), number of pregnancies, and types of deliveries. There were also no significant differences in the types of vulvovaginitis treatments tried previously.

Although evaluation of possible predisposing factors for VVC was difficult because of the clinical nature of the data, some differences emerged. *C. albicans* cases (23 of 30, 76.7%) were slightly more likely than *C. glabrata* cases (15 of 23, 65.2%, $\chi^2 p = 0.359$) or no-candida controls (24 of 43, 55.8%, $\chi^2 p = 0.067$) to have been sexually active in the past year; contraceptive practices were similar among both case groups and controls. No-candida controls (21 of 46, 45.7%) were more likely than *C. albicans* cases (eight of 34, 23.5%, $\chi^2 p = 0.042$) and *C. glabrata* cases (one of 18, 5.6%, $\chi^2 p = 0.002$) to use a combination of both sanitary napkins and tampons for menstrual protection. Finally, *C. glabrata* cases (10 of 13, 76.9%) were more likely than *C. albicans* cases (19 of 39, 48.7%, $\chi^2 p = 0.047$) or no-candida controls (20 of 53, 37.7%, $\chi^2 p = 0.292$) to ever have douched.

Discussion

Our study confirms the difficulties inherent in diagnosing women with a history of chronic vulvovaginitis (four or more episodes reported in the past year), as shown by the large numbers of women diagnosed as normal or with problems other than vulvovaginitis after referral to this specialty clinic. Some women initially diagnosed as normal may have become symptomatic and received a different diagnosis later. Others may have been suffering from a hypersensitivity or irritant vulvovaginitis that resolved when they discontinued all vaginal medications approximately six weeks prior to their visit. Another group may have confused physiologic leukorrhoea with abnormal discharge, a situation clarified at their clinic visit.

For all women diagnosed as normal or with a condition other than VVC, a negative yeast culture confirmed that VVC was not the appropriate diagnosis.

Women with *C albicans* VVC, *C glabrata* VVC and no candida were virtually indistinguishable by demographic characteristics and history. A complaint of painful sexual intercourse may suggest *C albicans* VVC, whereas women with underlying medical conditions and a shorter history of vulvovaginal complaints may have *C glabrata* VVC. These characteristics have not been reported by other researchers. We did not confirm previous reports that women with *C glabrata* VVC tend to be older.^{22 23}

We did not find physical examination to be particularly helpful in differentiating VVC due to *C albicans* from that due to *C glabrata*; however, other studies have found that *C glabrata* cases exhibit fewer and less severe symptoms.^{23 24} Reliance on KOH microscopy alone would have incorrectly identified about 30% of *C albicans* VVC cases and 57% of *C glabrata* VVC cases as negative for yeast. Only vaginal yeast cultures identified these false-negative cases, suggesting that cultures are useful in clarifying the diagnosis when the physical examination is consistent with VVC but KOH microscopy is negative. The higher proportion of false-negative *C glabrata* cases may be due to the lack of hyphae formation by this organism, making it more difficult to identify microscopically.^{25 26} Speciation of positive yeast cultures allowed us to differentiate *C albicans* and *C glabrata* VVC; speciation also facilitates the tailoring of therapeutics to the organism.¹³⁻²⁰

Our study was limited in size and has all the problems inherent in medical record review studies. Further, the study population is susceptible to selection bias due to complex, undefined referral patterns in the broader population; this may limit the generalisability of our results to women attending similar clinics and may create false associations in our comparisons. Moreover, the use of a retrospective case-control study design among a population with a long history of vulvovaginal complaints is problematic in that we cannot guarantee the temporal sequence of any associations and do not have any knowledge about the natural history of vaginal infection with various agents. However, this is the only controlled study to specifically address the role of vaginal yeast cultures in the diagnosis of chronic vulvovaginitis and VVC, and one of few to investigate differences in the clinical presentation of *C albicans* and *C glabrata* VVC.

In summary, we found that the presenta-

tion of women with a history of chronic vulvovaginitis to a vulvovaginitis specialty clinic was similar among groups receiving different diagnoses. As increasing numbers of women avail themselves of over-the-counter antifungals, it is particularly important that women seeking care for recurring VVC be adequately evaluated, with cultures used to verify the presence of yeasts and to exclude the possibility of infection with non-*C albicans* organisms.

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