Vulvovaginal Candidiasis in Postmenopausal Women: The Role of Hormone Replacement Therapy

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■ **Abstract**

Objective. This study aimed to explore the role of hormone replacement therapy (HRT) in susceptibility to vulvovaginal candidiasis (VVC) in a private vulval disease referral practice.

Methods. Between January 2009 and December 2010, 149 healthy, nondiabetic patients with vulvar conditions were compared for significant differences in vaginal swab result, age, and diagnosis between those using and not using HRT. Detailed clinical data were collected from those with VVC.

Results. The mean ages of the HRT (n = 70) and non-HRT (n = 79) groups were 62.5 and 62.5 years, respectively. Positive cultures for *Candida* were found in 34 (48.5%) of 70 patients on HRT and in 2 (3%) of 79 subjects not on HRT ($p < .001$). Culture-positive, clinical VVC was identified in 34 (49%) of 70 patients on HRT and in 1 (1%) of 79 patients not on HRT ($p < .001$). *Candida* species (32 *Candida albicans* and 2 *Candida glabrata*) were isolated from the 34 VVC patients, and of these, 23 (67%) had a history of recurrent or chronic candidiasis before menopause. All 34 had been previously treated with antifungal therapy without ceasing HRT and had been unresponsive to treatment or had relapse after treatment. In 27 (79%) of 34 patients, HRT was suspended during treatment. Of those who remained on HRT during treatment or resumed it after treatment, prophylactic antifungal treatment was initiated in 15 (44%) to prevent recurrence. All patients responded to the antifungal treatment provided HRT was suspended or prophylactic treatment was used.

Conclusions. Postmenopausal women taking HRT are significantly more prone to develop VVC than women who are not and those with VVC are likely to have been susceptible to it before menopause. ■

Key Words: *Candida*, vulva, estrogen, hormone replacement therapy, menopause

It has been our observation that, in healthy postmenopausal women, vulvovaginal candidiasis (VVC) is almost invariably seen in patients using estrogen hormone replacement therapy (HRT) and, conversely, not encountered in those who are not on HRT. A susceptibility of postmenopausal women on HRT to candidiasis relative to those not on HRT has been previously documented in 2001 [1]. To our knowledge, this specific association has not been explored since in the medical literature. As a result, many clinicians prescribing HRT may not be aware of VVC as a potential adverse effect.

This retrospective chart review examines a cohort of 149 healthy nondiabetic, postmenopausal women referred to a private dermogynecology practice, presenting with symptomatic vulvar conditions in whom a vaginal swab had been done because they exhibited signs of inflammation consistent with possible VVC. Of these women, 70 (47%) were on HRT and 79 (53%) were not. Our objectives were as follows: first, to determine whether there existed a difference in susceptibility to VVC between those on and not on HRT; and second, to examine the clinical characteristics of women within this cohort with a diagnosis of VVC, particularly

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with respect to their HRT status and response to antifungal treatment.

METHODS

The study was exempted from full ethics review because the collected data were drawn from a noninstitutionalized setting (private practice of a dermatologist and a gynecologist with a vulvar disease referral practice), and all data were deidentified.

All patients in the study were referred for diagnosis and management of symptomatic vulvar disease.

Health care providers at the pathology department of the practice were asked for a list of all women older than 45 years on whom a low vaginal swab had been performed during the period January 2009 to December 2010. Charts of these patients were reviewed to identify patients who met the following inclusion criteria:

Vaginal swab performed to confirm or exclude candidiasis because of symptoms of vaginitis, presence of discharge, or clinical evidence of inflammation.
At least 12 months postmenopausal
Not diabetic or immunosuppressed
In good general health
Presenting with chronic vulvar symptoms

We identified 149 patients who met these criteria and divided them into 2 groups: those on HRT, systemic, topical, or both, and those not on HRT.

Data were entered on an Excel 2007 spreadsheet (Microsoft Corp, Redmond, WA) documenting age at presentation, result of vaginal swab, and diagnosis group, defined as follows:

Inflammatory vulvar dermatoses (dermatitis, lichen planus, lichen sclerosus, psoriasis, VVC)
Vulvar pain syndromes
Desquamative inflammatory vaginitis
Drug eruptions
Others not included

Vulvovaginal candidiasis was defined as inflammatory, nonerosive, vulvovaginitis with symptoms including itch, soreness, dyspareunia, and discharge, with a positive culture demonstrating *Candida* from a low vaginal swab with subsequent resolution of signs and symptoms on antifungal medication. It should be noted that these patients were chronically symptomatic. In the past, VVC has been described as either acute or recurrent [2].

From the inflammatory dermatoses diagnosis group, patients with a diagnosis of VVC were identified, and further data were collected on these patients.

These data were entered on the spreadsheet, documenting age at presentation, age at menopause, duration and nature of symptoms, HRT used and duration of HRT, vaginal swab result, clinical examination, history of candidiasis before menopause, previous treatment and response to treatment, current treatment and response to treatment, ongoing use of HRT, and ongoing management.

Statistics

Data were analyzed using descriptive tables of the variables studied. Statistical analysis was calculated with SPSS statistical software (version 16.0; SPSS, Inc, Chicago, IL). The Fisher exact test and χ^2 test were used to detect significant differences between the HRT and non-HRT groups. $p \leq .05$ was considered significant.

RESULTS

A total of 149 patients were included in the study: 70 (47%) in the HRT group and 79 (53%) in the non-HRT group. All patients were at least 12 months postmenopausal; the mean age of the HRT group was 62.6 years (range, 47–78 y) and the mean age of the non-HRT group was 62.5 years (range, 51–86 y).

Clinical, microbiologic, and demographic characteristics of the study patients are summarized in Table 1.

Table 1. Demographic, Microbiology, and Clinical Diagnoses of Cohort (*n* = 149)

	On HRT *n* = 70	Not on HRT *n* = 79	*p*
Age, mean (range), y	62.6 (47–78)	62.5 (51–86)	NS
Symptomatic VVC, *n* (%)	34 (49)	1 (1)	<.001
Symptomatic VVC with concurrent other dermatoses, *n* (%)	3 (4%) (2 lichen sclerosus 1 lichen planus)	1 (1%) (lichen sclerosus)	NS
+ve swab for *Candida*, *n* (%)	34 (49)	2 (3)	<.001
−ve swab for *Candida*, *n* (%)	36 (51)	77 (98)	<.001
All vulvar inflammatory dermatoses,[a] *n* (%)	52 (74)	55 (70)	NS
Vulvar pain, *n* (%)	8 (11)	10 (12.6)	NS
Desquamative inflammatory vaginitis, *n* (%)	8 (11)	12 (15)	NS
Fixed drug eruption, *n* (%)	1 (1)	1 (1)	NS
Other, *n* (%)	1 (1)[b]	0	NS

n = 149.
[a]Includes patients with dermatitis, lichen sclerosus, psoriasis, lichen planus, and VVC.
[b]Patient presenting with vulvar squamous cell carcinoma.

Low vaginal swabs positive for *Candida* were found in 34 (49%) of 70 patients in the HRT group and in 2 (3%) of 79 in the non-HRT group ($p < 0.001$). Low vaginal swabs negative for *Candida* were found in 36 (51%) of 70 patients taking HRT and in 77 (97%) of 79 patients not taking HRT ($p < .001$).

Clinical signs and symptoms of VVC were identified in all 34 of the patients with positive cultures in the HRT group and in 1 (1%) of 79 patients in the non-HRT group ($p < 0.001$). There was no other significant difference between the 2 groups in age and distribution of clinical presentations. Of the inflammatory dermatoses group, however, 34 (65%) of 52 of those on HRT had VVC, which satisfied our case definition compared with 1 (2%) of 55 of those on the non-HRT group ($p < 0.001$). Three patients with VVC in the HRT group and one in the non-HRT group had a concurrent dermatosis: 3 lichen sclerosus and 1 lichen planus. The other 31 VVC patients did not have any other vulvar disease.

Clinical, microbiologic, and demographic characteristics of the group with VVC are summarized in Table 2. The mean age of this group was 61.26 years (range, 47–78 y) and mean age at menopause was 50.94 years (range, 44–57 y). All 34 patients were on HRT, with 17 (50%) being on systemic HRT and 17 (50%) being on topical HRT only. Eight of the patients on systemic HRT were concurrently using topical HRT. The mean duration of HRT was 6.2 years (range, 0.1–26 y) and mean duration of symptoms was 2.8 years (range, 0.1–17 y), so that, on average, there was an approximate 3.4-year gap between onset of HRT and onset of symptoms, indicating that patients were not incorrectly treated with HRT when in fact they had candidiasis as HRT preceded onset of symptoms by a substantial period in most patients. Cultures demonstrated *C. albicans* in 32 patients and *C. glabrata* in 2 patients. Of the 34 patients with VVC, 23 (67%) had a history of candidiasis before menopause. All patients with VVC who had been previously treated with antifungal therapy without ceasing HRT had been unresponsive to treatment or had relapse after treatment.

Table 2. Characteristics of Postmenopausal Patients With VVC (*n* = 34)

Age at presentation, mean (range), y	61.3 (47–78)
Age at menopause, mean (range), y	5.9 (40–58)
Duration of HRT, mean (range), y	6.2 (0.1–26)
Duration of symptoms, mean (range), y	2.8 (0.1–17)
Time from onset of HRT to onset of symptoms, mean (range), y	3.4 (0.1–9)
Organism at low vaginal swab, *n* (%)	
C. albicans	32 (94)
C. glabrata	2 (6)
HRT, *n* (%)	
Systemic	17 (50)
Topical	27 (50)
Topical + systemic	8 (24)
History of recurrent or chronic candidiasis before menopause, *n* (%)	23 (67%)
History of previous failure of antifungal treatment or relapse after treatment, *n* (%)	33/34 (100)[a]
Symptoms, *n* (%)	
Itch	26/34 (76)
Sore	26/38 (76)
Dyspareunia	18/24 (75)
Burning	3 (8)
Swelling	2 (7)
Splitting	2 (7)
Discharge	2 (7)
Dysuria	3 (8)
Signs, *n* (%)	
Erythema of labia minora and vagina	34 (100)
Edema of labia minora	5 (15)

[a]One patient had not previously received antifungal treatment.

Table 3. Treatment of Postmenopausal Patients With VVC (*n* = 34)

Medication	
Fluconazole 50–100 mg/d	18
Itraconazole 100 mg/d	11
Boric acid suppositories 600 mg/d[a]	2
Topical nystatin	2
Topical miconazole	1
Duration of treatment, mean (range), wk	5.3 (2–14)
Ongoing HRT, *n* (%)	
Ceased HRT at onset of antifungal treatment	27 (79.0)
Permanently ceased HRT	19 (59.0)
Resumed or continued HRT	15 (45.0)
Resumed or continued HRT who required ongoing antifungal treatment (3 mo minimum follow-up)	13 (38.0)

[a]Both patients with *C. glabrata* infection.

Details of treatment of patients with VVC are shown in Table 3. Most patients were treated with oral antifungal medication, using either fluconazole 50 to 100 mg/d or itraconazole 100 mg/d. Duration of treatment was guided by the time to achieve both symptomatic and objective normality and ranged from 2 to 14 weeks (mean, 5.3 wk). In 27 (79%) of 34 patients, HRT was suspended during treatment. Subsequently, 15 (44%) of 34 patients resumed or continued HRT, whereas 19 (56%) elected not to resume. Of those who remained on HRT or resumed it after treatment, 14 (93%) were continued on prophylactic antifungal treatment after recovery to prevent recurrence, and at the time of writing, 13 (86%) of these patients remain on this treatment with a minimum of 3 months of follow-up. All patients responded to antifungal treatment with loss of self-reported symptoms and objective loss of

inflammation and discharge. Patients who resumed HRT were advised that cessation of antifungal cover might result in relapse of symptoms.

DISCUSSION

Vulvovaginal candidiasis is a common problem that affects 70% to 75% of women at least once during their lives as a short-term event [2]. Recurrent VVC has been defined as at least 4 attacks per year [3, 4]; however, patients in this study were chronically symptomatic. Vulvovaginal candidiasis as a cause of chronic vulvovaginitis has not been formally defined, although in our experience in a dermogynecology practice, it is common.

The most commonly isolated strain in all forms of VVC is *C. albicans*, which accounts for 85% to 95% of reported cases, as was the case in our series [5]. Asymptomatic *Candida* colonization can evolve to symptomatic VVC with symptoms of itch, soreness discharge, dyspareunia, and clinical findings of swelling and erythema and the transformation from asymptomatic colonization to symptomatic vaginitis can be facilitated by host-related factors including the use of antibiotics, immunosuppression, frequent sexual intercourse, and diabetes mellitus [2]. Most patients we encounter with VVC before and after menopause are, however, otherwise healthy, and this was the group we specifically studied.

Exactly how a commensal organism causes symptomatic VVC is unknown. A study using an intravaginal challenge with *C. albicans* in healthy volunteers has demonstrated that susceptibility to candidiasis is associated with a brisk inflammatory response, whereas protection is associated with lack of inflammation and that patients with a previous history of candidiasis are those most likely to mount this response [6]. Such studies support the concept of an individual susceptibility to candidiasis. It is interesting that, in our cohort with VVC, a significant number (67%) of patients had self-reported premenopausal susceptibility. Genetic susceptibility to VVC may be playing a role, and this has been demonstrated previously in a murine model [7].

The research quoted here raises a new paradigm for understanding VVC. Previous studies have conceptualized this disease as a chronic infection and have searched for possible host immunodeficiency; however, this study suggests that symptoms relate to a local vaginal exaggerated inflammatory response: a host-mediated individual susceptibility to a commensal organism that is tolerated by most women. Vaginal cells in these patients are both lacking in anti-*Candida* activity and are also highly intolerant to the presence of *Candida*, generating an exaggerated immune response triggered by very low numbers of the organism [8].

Estrogen seems to play an essential permissive role in VVC. Clinical observations have shown that premenarchal and postmenopausal women rarely have VVC [1, 9] and that *Candida* is rarely isolated from the postmenopausal vagina [10]. Experimental data suggest that high concentrations of estrogen increase the glycogen content of vaginal epithelium, thus providing a carbon source for *Candida* [1, 11]. Estrogen-dependent transition of the epithelial cells from columnar to stratified squamous also increases susceptibility to adherence of *Candida* [12]. A *Candida* cytosolic receptor, which binds estrogen has been characterized, and this enhances the mycelia formation [13, 14].

In 2001, Dennerstein and Ellis [1] documented findings suggesting that postmenopausal women could become susceptible to candidiasis as a result of HRT. In their study of 339 consecutive patients, aged 55 or older presenting to a hospital dermogynecology clinic who all had a vaginal swab irrespective of signs of inflammation, 26% of those using estrogen had a positive vaginal swab for *C. albicans* as opposed to 4% in the group not using estrogen. Our study supports the findings of Dennerstein and Ellis. Our somewhat higher figure of 49% positive swabs in the HRT group reflects a differing methodology in that, given the financial restraints of a private practice, we took cultures only from women in whom we found inflammation and discharge (in whom we needed to exclude or confirm candidiasis) rather than all patients. A subsequent study in 2006 has shown that postmenopausal women on HRT have an altered vaginal microbial profile that may cause fungal and bacterial vaginitis [15]; however, we found no subsequent study specifically examining the role of HRT in candidiasis in postmenopausal women. It is therefore not surprising that there seems to be a low level of awareness in the medical community of this potential HRT adverse effect.

Our study demonstrates the importance of estrogen in the cause of VVC in postmenopausal women. All patients with VVC were using either systemic or topical estrogen or both. This cohort included those using topical estrogen only, so it is unlikely that this is a progesterone effect. This has been noted in a previous study [16]. In the group not taking HRT, clinical VVC was rarely encountered and was seen at a rate similar to that of the study by Dennerstein and Ellis. It would seem

that, in postmenopausal patients who do not take HRT, inflammatory vulvovaginitis is very unlikely to be due to candidiasis.

A recent study of the high-affinity estrogen binding protein of *C. albicans* in a murine model demonstrated that vaginal colonization is increased by estrogen [11]. The cellular target for the estrogenic modulation is unknown, and the role of the estrogen receptor has not been explored. Three isoforms of the estrogen receptor have been identified (alpha, beta, and gamma); however, only alpha and beta are found in the vaginal wall [17]. After menopause, the expression of estrogen receptors in vaginal tissues declines [18]. Hormone replacement therapy has been shown to upregulate this expression [19, 20], and this may explain why cessation of HRT facilitates treatment with antifungal agents.

In conclusion, we found that, in a group of postmenopausal women with symptomatic inflammatory vulvovaginitis, those on estrogen HRT were significantly more likely to have VVC than those not on HRT and two thirds of those women with VVC experienced it before menopause. This suggests that a combination of individual susceptibility and estrogenization is likely to be required for postmenopausal women to experience VVC, and otherwise healthy postmenopausal women not on HRT seem to be very unlikely to have VVC. In our study, postmenopausal women with VVC were universally using HRT and topical therapy was as likely to produce this effect as systemic therapy. We found that temporary cessation of HRT facilitated a successful treatment outcome from antifungal therapy and that women who continued or resumed HRT in most cases required ongoing antifungal prophylaxis.

In documenting this group, we hope to raise awareness of the role of HRT in postmenopausal women with VVC.

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