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ORIGINAL ARTICLE

Characterization of women with a history of recurrent vulvovaginal candidosis

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Background. To characterize history, signs, and symptoms in women with a history of recurrent vulvovaginal candidosis (RVVC) and who had consulted with symptoms generally associated with the condition.
Methods. Eighty-three women with a history consistent with RVVC were interviewed regarding 32 parameters and 10 signs found at the clinical examination were noted. *Candida* cultures were made from the introitus and the posterior vaginal fornix.
Results. Only in a few of the 43 women with and the 40 without a positive yeast culture could any of the many etiological factors that have been associated with RVVC be traced. Only two factors differed between the groups, namely yogurt intake, which was reported by 28 (68%) and 38 (95%) women in these groups, respectively. Vaginal douching was performed by 10 (23%) women in the *Candida*-positive group *and* by 17 (42%) women in the *Candida*-negative group. Pruritis and burning occurred in 31 (72%) and 22 (51%) of culture-positive patients, which was less frequent than in the culture-negative group, i.e. reported by 19 (47%) and 9 (22%) patients, respectively ($p = 0.022$ and $p = 0.007$). Edema ($p = 0.026$) of the vulva as well as erythema ($p = 0.019$) and edema ($p = 0.008$) of the vaginal mucosa, caseous discharge ($p = 0.016$), were found more often in the *Candida* culture-positive cases.
Conclusions. History and results of clinical examination of patients with RVVC are not enough to distinguish those who are culture-positive from those who are culture-negative for *Candida* from the genital tract.

Key words: recurrent vulvovaginal candidosis; symptoms; signs; history; pathogenesis

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Recurrent vulvovaginal candidosis (RVVC) is a common condition considered to affect 5–8% of all women, most often during reproductive age (1). Only in a small percentage of all RVVC cases, factors that have been associated with the condition, such as broad-spectrum antibiotic therapy, contraceptive use, pregnancy and uncontrolled diabetes mellitus, can be demonstrated (2). There have been a variety of proposals that one or more other factors can influence the rate of RVVC in a female population (3,4), but they have generally remained scientifically unproven (2).

Abbreviations:
RVVC: recurrent vulvovaginal candidosis; VVC: vulvovaginal candidosis.

The diagnosis of attacks of RVVC in routine health care is often false (3), even if based on extensive history taking and clinical findings. Thus, in only approximately half or less of such cases, *Candida* can be recovered from the genital tract (5,6). Eckert and co-workers (7) could only identify *Candida* in vaginal cultures in 28% of 554 women with symptoms regarded consistent with '*Candida* vaginitis'.

The present investigation was undertaken to study in which respects, if any, women with a history of RVVC and who had current symptoms consistent with vulvovaginal candidosis (VVC), and who proved positive for *Candida* from the genital tract, differed from those who were culture-negative for such yeasts. A comparison was also

made with a cohort without any history of VVC/RVVC or any such current problems. Extensive history taking, a pelvic examination and microbiological tests for *Candida* were performed. We also discuss the occurrence of some factors in our patients that have been regarded to trigger attacks of RVVC.

Materials and methods

Women with a history of RVVC

The 83 women studied had attended the outpatient department of the University maternity hospital No. 3, Kiev, Ukraine, from October 2000 to May 2001, because of current genital symptoms suggestive of VVC The patients enrolled in the study had either been referred to the investigators by other gynecologists in the city or had consulted directly at the clinic. They had all a history assuming that they had had at least four attacks of VVC during the last year, i.e. they fulfilled the criteria for RVVC (2). The age range of the women studied was 17–42 years. The study group was divided into those who were *Candida* culture-positive (43 cases) and *Candida* culture-negative (40 cases) from the genital tract. The mean age of women of the *Candida* culture-positive and culture-negative group was 26.1 and 25.3 years, respectively.

The women enrolled in the study had given written consent for their participation. The study was approved by the institutional review board.

History taking

The women were asked for current symptoms and examined for any pathological genital signs; in all 16 parameters were noted. A structured interview, in all covering 32 possible etiological factors of RVVC, was performed. The patients had at least once, but generally several times, presented with a vaginal smear showing *Candida* morphotypes, i.e. blastoconidia and/or pseudohyphae.

Sampling and laboratory tests

Samples from the introitus and the posterior vaginal fornix were collected and cultured on Sabouraud (Beckton Dickinson®, Baltimore, Maryland USA) and chromogenic agar (CHROMagar, Paris, France). Indicator sticks measured the pH of vaginal secretions (Merck KGaA, Darmstadt, Germany).

Women without any history or current symptoms suggestive of VVC/RVVC

A group of 136 women without any history or any current complaints suggesting either VVC or RVVC were interviewed using the same questionnaire as in the above-mentioned women with a history of RVVC No gynecologic examination or laboratory tests were made in this group of women. The age range in this cohort was also 17–42 years (mean age 25.2 years).

Statistics

Data were analyzed by means of the SPSS (LDC, Lund) 10.0 statistical software, and the χ^2 and Fisher's exact test. A p-value < 0.05 was considered significant.

Results

History

Table I shows anamnestic data in the two groups of symptomatic patients with and without a confirmed genital *Candida* infection *and* in the healthy comparison group. Women with RVVC reported a history of gynecologic diseases more frequently than women in the healthy comparison group.

Table II shows the history in the two symptomatic groups. Only two factors differed between the groups, namely yogurt intake, which was reported by 28 (68%) and 38 (95%) women in these groups, respectively. Vaginal douching was performed by 10 (23%) women in the *Candida*-positive group and by 17 (42%) women in the *Candida*-negative group. The corresponding figures in the comparison group of healthy women were 128 (94%) and 17 (12%), respectively.

Parameters concerning partner relations and contraception use in the three study groups are shown in Table III. In those with a positive yeast culture, intercourse for the first time had taken place at a mean of 4.5 years (range 0.5–17) before enrollment in the study. In the culture-negative group, the corresponding figure was 3.6 years (range 0.5–17) ago.

When asked whether the patients believed that the onset of their 'RVVC problems' had occurred in conjunction with any specific event, the following most frequent answers were obtained: during or shortly after a course of antibiotic therapy (7 cases), during pregnancy (4 cases), and shortly after having intercourse for the first time (4 cases). The corresponding figures in the culture-negative group were four, seven, and four, respectively. Only single patients in each of the groups believed that their problems started after an experience of severe stress or during a period of particularly warm or humid weather. Also, other uncommon proposals were onset after wearing too tight clothes, after iatrogenic measures or because they had suffered

Table I. Characterization of *Candida* culture-positive and culture-negative women with a history of recurrent vulvovaginal candidosis (RVVC) and who had consulted because of a new attack of the condition as well as a comparison group of women with no history of complaints consistent with a genital *Candida* infection

Parameters studied	*Candida* culture- positive ($n=43$)	*Candida* culture- negative ($n=40$)	Control group ($n=136$)	*p*-value
Age	26.1	25.3	25.2	n.e.
Gravidity	1.6	1.1	0.8	n.e.
Parity	0.6	0.35	0.3	n..e.
Prior sexually transmitted infection(s)	11 (26%)	11 (27%)	0	n.e.
Allergy	9 (21%)	14 (35%)	25 (18%)	0.001
Gynecologic disease(s)	19 (44%)	12 (30%)	4 (3%)	0.004
Socio-economic situation				
severe	4 (9%)	3 (7%)	n.e.	1.000
satisfactory	23 (54%)	18 (45%)	n.e.	0.440
good	16 (37%)	19 (48%)	n.e.	0.343

n.e.: not estimated.

Table II. Some factors proposed in the literature that trigger attacks of RVVC in the *Candida* culture-positive and culture-negative cases studied and in the controls with no history or current symptoms suggestive of a genital *Candida* infection

Parameters	*Candida* culture- positive ($n=43$)	*Candida* culture- negative ($n=40$)	Control group ($n=136$)	*p*-value
Antibiotic use last month	7 (16%)	5 (12%)	0	0.001
Wear of synthetic underwear	22 (51%)	22 (55%)	46 (34%)	0.019
Wear of tight clothes	26 (60%)	26 (65%)	65 (48%)	0.093
Washing underwear at $\leq 60°C$	4 (9%)	6 (15%)	39 (29%)	0.018
Habit of vaginal douching	10 (23%)	17 (42%)	17 (12%)	0.001
Taking a hot bath	22 (51%)	19 (47%)	56 (41%)	0.467
Tampon user	16 (37%)	20 (50%)	38 (28%)	0.030
Panty-liner user	17 (40%)	21 (52%)	58 (43%)	0.445
Smoker	17 (40%)	11 (27%)	39 (29%)	0.362
Intake of a lot of sweets	17 (40%)	22 (55%)	111 (82%)	0.001
Yogurt consumer	28 (65%)	38 (95%)	128 (94%)	0.001

Table III. Sexual practice and contraceptive use in the patients with a history of RVVC and in the healthy comparison group

Parameters	*Candida* culture- positive ($n=43$)	*Candida* culture- negative ($n=40$)	Control group ($n=136$)	*p*-value
Sexual debut at ≤ 17 years	16 (37%)	8 (20%)	35 (26.%)	0.184
Mean age at sexual debut	18.1	18.8	19.3	
Oral sex, regularly	23 (53%)	26 (62%)	36 (26%)	0.001
Anal sex, regularly	5 (12%)	10 (25%)	2 (1%)	0.001
Masturbate, regularly	7 (16%)	8 (20%)	10 (7%)	0.046
Sex during menstruation	7 (16%)	13 (32%)	20 (15%)	0.035
Mean no. of life-time partners	2.9	4.1	3	
Oral contraception user				
estrogen content	0	0	0	
high (>35rng)				
medium (≤ 35 mg >20 mg)	3 (7%)	1 (2%)	3 (2%)	0.289
low (≤ 20 mg)	1 (2%)	0	0	0.128
gestagen	1 (2%)	0	0	0.128
Spermicide user	1 (2%)	1 (2%)	2 (1%)	0.879
Partner condom user	19 (44%)	27 (67%)	61 (45%)	0.033
IUD (non-hormonal releasing)	1 (2%)	0	3 (2%)	0.633

Table IV. Symptoms in the *Candida* culture-positive and culture-negative cases with a history of recurrent vulvovaginal candidosis (VVC)

Symptoms	*Candida* culture- positive ($n=43$)	*Candida* culture- negative ($n=40$)	*p*-value	OR	CI
Vulvovaginal pruritis	31 (72%)	19 (47%)	0.022	2.9	1.1–7.1
irritation	22 (51%)	9 (22%)	0.007	3.6	1.4–9.4
unpleasant odour	9 (21%)	10 (25%)	0.659	0.8	03–2.2
dyspareunia	19 (44%)	14 (35%)	0.393	1.5	0.6–3.6
Urinary dysuria	17 (40%)	6 (15%)	0.013	3.7	1.3–10.7
burning at micturation	22 (51%)	9 (22%)	0.007	3.6	14–9.4
Intestinal diarrhea	2 (5%)	3 (7%)	0.668	0.6	0.1–3.8
constipation	8 (19%)	6 (15%)	0.661	1.3	0.4–4.1

Table V. Character of the vaginal discharge in the *Candida* culture-positive and culture-negative cases with a history of RVVC

Characteristics	*Candida* culture- positive ($n=43$)	*Candida* culture- negative ($n=40$)	*p*-value	OR	CI
Mucosus	10 (23%)	18 (45%)	0.036	0.4	0.1–1.0
Caseous	23 (53%)	11 (27%)	0.016	3.0	1.2–7.6
Aqaeous	2 (5%)	1 (2%)	0.527	1.9	0.2–21.8
Foamy	1 (2%)	1 (2%)	0.735	0.9	0.1–15.4
White	41 (95%)	38 (95%)	0.941	1.1	0.1–8.0
Yellow	2 (5%)	2 (5%)			
Gray	0	0			
Scanty	1 (2%)	3 (7%)	0.281	0.3	0.03–3.0

from a hormonal disorder. Twenty-six of the *Candida* culture-positive (50?) and 22 (55%) of the culture-negative patients could not associate the onset of RVVC to any specific event.

Symptoms

Itching, an irritating feeling in the vulva and dysuria, occurred significantly more often in those with than without a positive *Candida* culture (Table IV). Otherwise, there were no statistical differences between the patients with regard to the symptoms registered.

Signs

The amount and the color of the vaginal discharge in the two groups with different culture results did not differ ($p>0.05$), although a caseous discharge was more common in the culture-positive group ($p=0.016$) (Table V). Edema of the vulva ($p=0.026$), erythema ($p=0.019$) and edema ($p=0.008$) of the vaginal mucosa were, however, more common in the culture-positive group (Table VI).

Discussion

Obviously, there is an age-related physiological influence of sex hormones on the prevalence of RVVC, including the hormonal changes occurring during pregnancy (8).

However, in only 6% of our cases, first onset of symptoms suggestive of an attack of VVC had occurred during pregnancy. RVVC is uncommon before menarche and less common after than before menopause, although an increased prevalence is seen in women given hormone replacement therapy. The period in life we choose to study represented most of the reproductive age, i.e. we enrolled women 17–42 years of age.

Early start of sexual life has been regarded as a predisposing factor for RVVC (9). However, the mean age for first intercourse in our *Candida* culture-positive group (18. 1 years) did not differ from that of the culture-negative women (18. 8 years). Neither did it differ from the mean age (19.3 years) in the healthy comparison group.

Use of high estrogen-containing oral contraceptives has by some authors been found to trigger attacks of RVVC (10,11), while others have not found colonization by *Candida* to be more common in such users than non-users (12). In the present study, only a few used 'the pill', i.e. five (12%) of the culture-positive and only one (2.5%) of the culture-negative women. Spermicides were not used by more than one patient in each of the two groups from which *Candida* cultures had been

Table VI. Signs in the *Candida* culture-positive and culture-negative cases with a history of recurrent VVC

Signs	*Candida* culture- positive ($n=43$)	*Candida* culture- negative ($n=40$)	*p*-value	OR	CI
Perianal area normal findings	26 (60%)	29 (72%)	0.247	0.6	0.2–1.5
erythema	16 (37%)	10 (25%)	0.231	1.8	0.7–4.6
edema	4 (9%)	0	0.117	2.0	1.6–2.6
dermatitis	3 (7%)	1 (2%)	0.617	2.9	0.3–29.3
scratches	3 (7%)	0	0.242	2.0	1.6–2.5
Vulva normal findings	26 (60%)	20 (50%)	0.338	1.5	0.6–33.7
erythema	17 (40%)	19 (47%)	0.464	0.7	0.3–1.7
edema	6 (14%)	0	0.026	2.1	1.7–2.6
fissures	3 (7%)	0	0.242	2.0	1.6–2.5
Vagina normal mucosa	9 (21%)	18 (40%)	0.019	0.3	0.1–0.8
erythema	34 (79%)	22 (55%)	0.019	3.1	1.2–8.1
edema	7 (16%)	0	0.008	2.1	1.7–2.7

made. None utilized a diaphragm, which is still another contraceptive method that has been associated with RVVC (13–15).

A number of other behavior-related factors have been assumed, but hardly proven to trigger RVVC (2). These factors include a high frequency of intercourse and multiple partners as well as oral and anal sex (9,13,17,18). However, we did not find such sexual practice to differ between the women in our study who were and were not found to harbor *Candida* (19). Unproven triggering factors of RVVC include wearing of tight-fitting clothes and of synthetic underwear (12) and wearing underwear washed at a temperature unable to kill *Candida* organisms (20). Certain hygiene procedures have also been considered to be associated with genital *Candida* infections, including vaginal douching. The latter was a significantly more common practice (with water) among our *Candida* culture-negative than culture-positive women (Table II).

There is firm evidence that poor glucemic control in diabetes mellitus patients can trigger RVVC attacks (21). Goswami and co-authors (22) found a higher prevalence rate of VVC in diabetic women (46%) than in healthy controls (23%) ($p = 0.025$). None of our patients had, however, diabetes mellitus. Overweight is associated with diabetes and with *Candida* skin infections (2). Only one of our patients with a history of RVVC was obese. Intake of rapid carbohydrates is believed to be able to induce new attacks of RVVC (21,22). However, available data are inconsistent regarding the impact of certain diets on RVVC (2).

There are a number of hypotheses that immune pathogenetic mechanisms can explain RVVC, e.g. inability of the cell-mediated immune system to effectively limit growth of *Candida* (23). The current study did not, however, allow valuation of the importance of an immune dysfunction in our patients, but the severely impaired cellular immunity in advanced AIDS cases is associated with both general and vaginal *Candida* infections.

VVC/RVVC are not useful early markers of HIV infection (24); HIV-infections had not been diagnosed in any of our patients.

Recurrences of VVC have been blamed on therapeutic failure due to antifungal resistance (25). Recently, we described a new resistance mechanism in one of the drugs often used to treat RVVC cases, i.e. fluconazole. There is an efflux of the drug in fluconazole-resistant *Candida* strains (26). However, in our study population fluconazole had only been used by a few of our patients.

The high rate, e.g. 52%, of negative *Candida* cultures in our patients with a history of RVVC, and who had symptoms and signs that could have suggested that they had a current genital infection, points to the difficulty in identifying 'true' RVVC cases. That is, to track down such 'RVVC' patients, who really have a genital infection by *Candida*. The use of yeast culture and patient-close diagnostic tests for the detection of *Candida* cell morphotypes, i.e. of blastoconidia and/or pseudohyphae, in wet mount or stained vaginal and/or introital smears [as we have reported elsewhere (16)], may also help to identify Candida-infected persons. Thus, it is essential to stress that a microbiologic diagnosis is necessary to identify those cases that have a *Candida* infection that one generally associated with the condition among patients with a history of RVVC and who consult with symptoms and signs. Episodes believed to represent RVVC must be classified as 'idiopathic' cases, as factors that have been associated with RVVC can only be demonstrated in a minority of them.

References

1. Sobel JD. Epidemiology and pathogenesis of recurrent vulvovaginal candidlasis. Am J Obstet Gynecol 1985; 152: 924–35.
2. Mårdh P-A, Rodrigues A, Gene M, Novikova N, Martinez-de-Oliveira J, Guashino S. Facts and myths on recurrent vulvovaginal candidosis – a review of epidemiology, pathogenesis, diagnosis and therapy. Int J STD & AIDS 2002; 13: 522–39.
3. Sobel JD. Recurrent vulvovaginal candidiasis. New Engl J Med 1986; 315: 1455–8.
4. Elegbe IA, Elegbe I. Quantitative relationships of *Candida albicans* infections and dressing patterns in Nigerian women. Am J Public Health 1983; 73: 450–2.
5. Ledger WL. Current problems in the diagnosis and treatment of *Candida* vaginitis. Ital J Obst Gyn 1999; 11: 25–9.
6. Novikova N, Rodrigues A, Mårdh P-A. Can the diagnosis of recurrent vulvovaginal candidosis be improved by the use of vaginal lavage samples and cultures on chromogenic agar. Inf Dis Obstet Gynecol 2002; (in press).
7. Eckert LO, Hawes SE, Stevens CE, Koutsky LA, Eschenbach DA, Holmes K-K. Vulvovaginal candidiasis: clinical manifestations, risk factors, management algorithm. Obstet Gynecol 1998; 92: 757–62.
8. Cotch M, Hillier SL, Gibbs RS, Eschenbach DA for the Vaginal Infections Prematurity Study Group. Epidemiology and outcomes associated with moderate to heavy *Candida* colonization during pregnancy. Am J Obstet Gynecol 1998; 178: 374–80.
9. Hellberg D, Zdolsek B, Nilsson S, Mårdh P-A. Sexual behaviour of women with repeated episodes of vulvovaginal candidlasis. Eur J Epidemiol 1995; 11: 525–9.
10. Fidel PU, Cutright J, Steele C. Effects of reproductive hormones on experimental vaginal candidiasis. Infect Immun 2000; 68: 652–7.
11. Spinillo A, Capuzzo E, Nicola S, Baltaro F, Ferrari A, Monaco A. The impact of oral contraception on vulvovaginal candidiasis. Contraception 1995; 51: 293–7.
12. Schmidt A, Noldechen CF, Mendling W, Hatzmann W, Wolff MH. Oral contraceptive use and vaginal candida colonization. Zentralbl Gynakol 1997; 119: 545–9.
13. Geiger AM, Foxman B. Risk factors in vulvovaginal can-

didiasis: a case-control study among college students. Epidemiology 1996; 7: 182–7.
14. Hooton TM, Roberts PL, Stamm WE. Effects of recent sexual activity and use of a diaphragm on the vaginal microflora. Clin Infect Dis 1994; 19: 274–8.
15. McGroarty JA, Soboh F, Bruce AW, Reid G. The spermicidal compound nonoxynol-9 increases adhesion of *Candida* species to human epithelial cell in vitro. Infect Immun 1990; 58: 2005–7.
16. Novikova N, Yassievich E, Mårdh P-A. Microscopy of stained smears of genital secretion in the diagnosis of recurrent vulvovaginal candidosis. Int J STD & AIDS 2002; 13: 318–22.
17. Spinillo A, Carratta L, Pizzoli G, Lombardi G, Cavanna C, Michelone G et al. Recurrent vaginal candidiasis. Results of a cohort study of sexual transmission and intestinal reservoir. J Reprod Med 1992; 37: 343–7.
18. Otero L, Palacio V, Carrero F, Mendez FJ, Vazquez F. Vulvovaginal candidiasis in female sex workers. Int J STD & AIDS 1998; 9: 526–30.
19. Mårdh P-A, Novikova N, Stukalova E. Colonization by Candida of extragenital sites in cases of recurrent vulvovaginal candidosis. Br J Obstet Gynecol 2002; (in press).
20. Rashid S, Collins M, Corner J, Morton RS. Survival of Candida albicans on fabric after laundering. Br Vener Dis 1984; 60: 277.
21. Odds FC. Factors that predispose the host to candidosis. In: Odds FC (ed.): Candida and candidosis. Baltimore: University Park Press, 1988: 93–114.
22. Goswami R, Dadhwal V, Tejaswi S, Datta K, Paul A, Haricharan RN et al. Species-specific prevalence of vaginal candidiasis among patients with diabetes mellitus and its relation to their glycaemic status. J Infect 2000; 41: 162–6.
23. Witkin SS, Jerernias J, Ledger WL. Vaginal eosinophils and lgE antibodies to Candida albicans in women with recurrent vaginitis. J Med Vet Mycol 1989; 27: 57–8.
24. Foxman B. The epidemiology of vulvovaginal candidlasis; risk factors. Am J Public Health 1990; 80: 329–31.
25. Lynch ME, Sobel JD, Fidel PL. Role of antifungal drug resistance in the pathogenesis of recurrent vulvovaginal candidiasis. J Med Vet Mycol 1996; 34: 337–9.
26. Pina-Vaz C, Sansonetty F, Rodrigues AG, Martinez-de-Oliveira J, Fonseca AF, Mårdh P-A. Antifungal activity of ibuprofen alone and in combination with fluconazole against Candida species. J Med Microbiol 2000; 49: 831–40.

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