
Recurrent vaginal candidiasis and allergic rhinitis: a common association

Paula S A Moraes, MD

Background: In a recent series of studies, it has been shown that hypersensitivity is an important factor in recurrent vaginal candidiasis and several referring gynecologists have been asking for our support in the evaluation of women with regard to the possibility of local vaginal hypersensitivity. This study was instituted because, since the first anamnesis, a high incidence of perennial allergic rhinitis, as well as family allergies have been observed in these patients.

Objective: To study the association between recurrent vaginal candidiasis and perennial allergic rhinitis, and to explore the allergic characteristics of the patients and of the disease.

Methods: For 28 months, we have prospectively studied 95 patients with recurrent vaginal candidiasis referred by gynecologists to a private allergy practice. All of them were unresponsive to all other modalities of therapy, and had no diabetes or immunodeficiency diseases. As a control group, we studied 100 women, who came to the allergy office for other reasons, and had no recurrent vaginal candidiasis. All of these 195 women were submitted to a standard allergy medical history, a complete physical examination, and immediate skin tests with a standard battery of inhalant allergens and *Candida albicans*. The incidence of allergic diseases in the two groups was compared.

Results: Sixty-four patients with recurrent vaginal candidiasis also had allergic rhinitis (71%), while in the control group the incidence of this pathology was 42%. The difference was considered statistically significant, according to the software Epi info ($P < .0001$). The study (1) did not show an association between recurrent vaginal candidiasis and asthma and (2) indicated that patients with recurrent vaginal candidiasis have a high incidence of skin tests positive to inhalant allergens (50%), to *Candida albicans* (55%), and a high incidence of family history of allergies (73%). In control women, the incidence of skin test positive to inhalant allergens was 72% and to *Candida albicans*, 10%. There was a family history of allergies in 61% of women.

Conclusions: The data demonstrate that recurrent vaginal candidiasis is statistically associated with perennial allergic rhinitis and that many of these women with recurrent vaginal candidiasis tend to be atopic.

Ann Allergy Asthma Immunol 1998;81:165–169.

INTRODUCTION

Recurrent vaginal candidiasis (at least four documented episodes of candidal vaginitis during 12 months) is a worldwide problem affecting millions of women. The reasons why some women—in the absence of classic predisposing factors such as diabetes, immunosuppression, pregnancy, recent antibiotic or steroid use—are suscepti-

ble to recurring vaginal infections remain unclear.¹

In 1990, an article published in the *American Journal of Obstetrics and Gynecology* on recurrent allergic vulvovaginitis made some gynecologists start referring these patients for an allergic evaluation more frequently.² Since the first anamnesis, we have observed a high incidence of perennial allergic rhinitis and family history of allergic diseases allergies. For this reason, we decided to perform a prospective study, in which some clinical and

allergic aspects of these women were analyzed.

The involvement of the genital tract of women in allergic reactions to pollen was described many years ago. In 1948, Mitchell et al³ reported on a series of eight children with typical upper respiratory pollinosis as well as vulvovaginitis. Berman⁴ in 1964, also reported 16 similar cases.

Other authors reported the findings of respiratory allergies associated with recurrent candidiasis.^{5,6} In 1988, Witkin et al⁷ identified *C. albicans* and pollen-specific IgE in the vaginal wash from patients with recurrent vaginal candidiasis. He laments the low importance that has been given to this subject in the literature, both in gynecology as well as in allergy.

In 1995, Dhaliwal and Fink⁸ described a 10-year-old child with nasal and vaginal symptoms due to pollen. In 1998, Moraes⁹ reported a child with persistent vaginitis and perennial allergic rhinitis, describing, to our knowledge, the first case of putative house dust mite-induced vaginitis.

The aim of this study was to explore the association between recurrent vaginal candidiasis and perennial allergic rhinitis.

METHODS

This study was prospectively conducted for 28 months. During this period, 95 women from 18 to 57 years old with recurrent vaginal candidiasis were studied. All were referred to a private allergy practice by their gynecologists. It was a random sample, and not of previously known allergic women.

Every patient had at least four episodes during the previous year, and were referred because all other treatment modalities had failed. All patients had established positive *C. albi-*

Paula Moraes, Felipe dos Santos, 204/801; CEP:30-180-160 Belo Horizonte, MG, Brazil.

cans vaginal cultures. None had diabetes mellitus, anemia, AIDS, or thyroid disease. Nor were any using antibiotics, corticosteroids, or immunosuppressive drugs for any disease. Ninety-six percent were sexually active.

A control group was recruited from among patients seen in the allergist's office during the same period, but for other reasons. These women were also 18 to 57 years old, sexually active, and not suffering from recurrent vaginal candidiasis. Women who came to the office suffering from non-allergic diseases (chronic obstructive lung disease, psoriasis, vasomotor rhinitis, etc) did not enter the control group.

We used standard allergy & medical histories to obtain information from each patient regarding their symptoms, the frequency and intensity of episodes, triggering factors, and familial allergic history. All women underwent physical examinations and immediate skin prick tests with a standard battery of inhalant allergens (Laboratório Merck, Rio de Janeiro) and *Candida albicans* (Laboratório da Fundação Ataulpho de Paiva-Rio de Janeiro). A histamine (1 mg/mL) skin test was also applied in all cases. A wheal 3 mm greater than control with erythema was considered positive.

Fisher's Exact Test was used to analyze categorical variables. Kruskal-Wallis's test was used to compare medians. A chi-square test was used to test the significance of differences between groups. *P* values of .05 or less were considered to indicate statistical significance. Data were analyzed using Epi Info (USC Incorporated, Stone Mountain, GA).¹⁰

RESULTS

Table 1 illustrates the general characteristics of allergy histories and immediate skin tests in 95 patients with recurrent vaginal candidiasis and in the control group.

The mean age was similar between the cases and the controls (31.9 ± 7.9 years versus 34 ± 9.9 years).

This difference was not statistically significant (Kruskal-Wallis = 1.7; *P* = .1716).

Table 1. General Characteristics of 95 Patients with Recurrent Vaginal Candidiasis and of 100 Control Patients

	Candidiasis Group		Control Group	
	n	%	n	%
Family history of allergy	70.0	73.0	61.0	61.0
History of rhinitis	64.0	67.3	27.0	27.0
History of rhinitis/asthma	4.0	4.0	15.0	15.0
History of asthma alone	0	0	10.0	10.0
Sexual activity	92.0	96.0	100.0	100.0
Sexual intercourse as the main triggering factor	68.0	71.0	0	0
Immediate skin test positive to mites	51.0	53.0	72.0	72.0
Immediate skin test positive to <i>C. albicans</i>	55.0	68.0	10.0	10.0
Total	95		100	

Figure 1 presents the incidence of allergic diseases in both groups, which shows an accumulation of cases of rhinitis in the candidiasis group (67.3%). There is a relative lack of other allergic diseases: only four patients in this group suffered from asthma associated with rhinitis (4.2%) and none suffered from asthma alone. Conversely, we found rhinitis present in 42% (27% rhinitis alone + 15% rhinitis associated with asthma) of women in the control group but only 10% had asthma alone.

Table 2 illustrates the incidence of rhinitis in both groups. Statistically, there is a strong association between the recurrent vaginal candidiasis and the rhinitis (*P* < .0001).

Table 3 shows the incidence of asthma observed in both groups. There

Table 2. Incidence of Allergic Rhinitis in 95 Patients with Recurrent Vaginal Candidiasis and in 100 Control Women

	Candidiasis Group	Control Group	Total
Rhinitis present	68	42	110
Rhinitis absent	27	58	85
Total	95	100	195

Chi square test = 16.15 *P* < 0.0001

is a strong statistical association between the presence of recurrent vaginal candidiasis and the absence of asthma (*P* = .005).

DISCUSSION

Candida albicans is a common commensal and opportunistic pathogen of

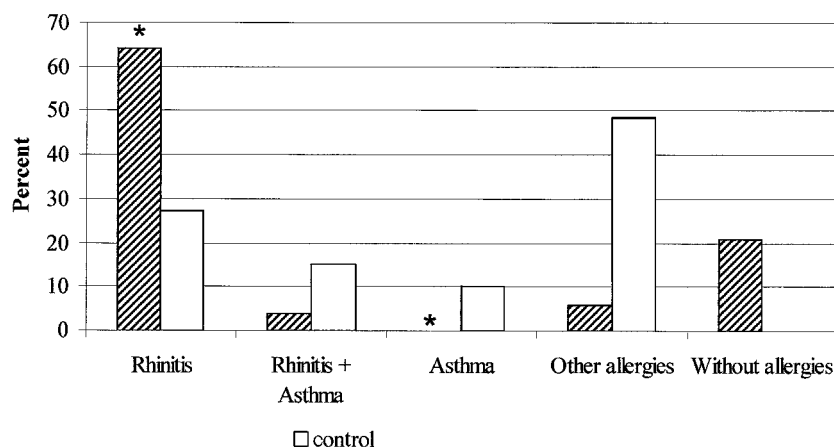


Figure 1. Incidence of allergic diseases in 95 women with recurrent vaginal candidiasis and in 100 control women. ▨ = recurrent candidiasis and □ = control. * Statistically significant values.

Table 3. Incidence of Asthma in 95 Patients with Recurrent Vaginal Candidiasis and in 100 Control Women

	Candidiasis Group	Control Group	Total
Asthma present	4	25	29
Asthma absent	91	75	166
Total	95	100	195

Fischer's exact test, $P = .0001$.

human microbial flora. It is found mainly on the mucous membranes of the gastrointestinal tract and vagina. *Candida albicans* is a dimorphic microorganism, gram-positive, of low virulence that can exhibit either a yeast-like or a fungal morphology. Most adults develop physiologic defense mechanisms, which control the growth and diffusion of such yeast.

In spite of having been identified in 1834, the most interesting period in the history of *Candida* infection began in the 1940s, when antibiotics were introduced into clinical use. Since then, previously undocumented manifestation of this infection have appeared and the incidence of practically all forms of *Candida* infections has risen abruptly.¹¹

Approximately 20% of women harbor *C. albicans* in the vagina without symptoms. During the yeast-to-fungus transition, *C. albicans* acquires the ability to invade mucosal epithelia, giving rise to the infection, which is characterized by symptoms such as severe genital itching, discharge, burning and dyspareunia. The mechanisms by which the conversion from a normal commensal to its pathogenic variant takes place are poorly understood. It has never been demonstrated that the insertion of a few spores of *C. albicans* into a healthy vagina can cause any harm.¹¹

Vaginal candidiasis is the most frequent of vaginal infections, occurring in 75% of women at some point in their lives. Thirty percent of those will have more than one episode. Close to 5%, will develop a chronic clinical condition, of difficult therapeutical ap-

proach, which may last several years, and that will become a frustrating entity for both patients and physicians.^{2,11}

Some clinical conditions, such as pregnancy, diabetes, thyroid disease, anemia, and cellular immunodeficiency may facilitate recurrent candidiasis. Iatrogenic factors, due to the use of antibiotics, corticosteroids, oral contraceptives and immunosuppressive agents also act in the same way. Nevertheless, the overwhelming majority of women with this chronic problem are healthy and lack these factors.¹ The findings of positive cultures in the penis of 25% of male partners of women suffering from recurrent candidiasis may be more a consequence than a cause of the vaginal infection. It is probably not transferable sexually, so that the treatment of male partners has not affected the outcome of treatment in carefully controlled double-blind studies.¹²

According to several publications, *C. albicans* is also a potent allergen in some situations. Both the protein and carbohydrate fractions of the yeast contain allergens.^{13,14} In spite of the controversy over whether or not *C. albicans* plays a role in causing allergies,¹⁵ from a practical point of view, it has been suggested that the yeast is as an important causative allergen in bronchial asthma, rhinitis, chronic urticaria atopic dermatitis, recurrent vaginitis, and balanitis.¹⁶⁻¹⁸

The present study analyzed women, in whom all modalities of treatment had failed. Some had been given high doses of ketoconazole for a long period of time. Almost all of them had been evaluated by at least two gynecologists. The women were not taking oral contraceptives. Some of these women began to show psychologic disorders as a result of dealing with the disease for a long time. The male partner of all of these women had also been treated with local and systemic antifungal agents.

The majority of patients reported allergic nasal symptoms in their medical histories. The fact that the allergic complaints, when present, were almost always of nasal origin, aroused our cu-

riosity and motivated the present study. Are we facing a syndrome (rhinitis and vaginitis)? Is there any possibility that there is an etiologic or a therapeutic link between rhinitis and vaginitis that could give some relief to these women? Since most of these women come from families with histories of allergy, why don't they suffer from asthma? The data suggest that atopy and rhinitis are risk factors for recurrent vaginitis, but asthma does not seem to be correlated with vaginal candidiasis. Is there an alternation of symptoms here? It seems when the patient has asthma, she will not develop *Candida* vaginitis. These observations transport us to the past, when the first practicing allergists used to observe the alternation of symptoms more frequently.

Another hypothesis arising from the interpretation of our results is that, although patients referred were a random sample, it's possible the gynecologist tended to refer women with histories of allergic disease. Of course, allergic rhinitis is the most frequent of such diseases.

It must be made very clear that, in this study, we are not referring to the so-called "Candida hypersensitivity syndrome," popularized by Truss and Crook in the *Yeast Connection*.¹⁵ Instead, we refer to a specific association between nasal and vaginal symptoms in atopic women suffering from recurrent candidiasis. These findings led us to conclude that allergy is a predisposing factor for chronic or recurring candidiasis.

The association between the nose and the reproductive system is not a new in medicine. Hipocrates had already observed 2,000 years ago, that the nasal mucosa appears edematous and reddened during menses and pregnancy.¹⁹ In animals, and probably also in humans, the olfaction is directly associated with the sexual impulse. From a neurophysiological point of view, according to some authors, fibers from the olfactory nerve join at the rhinencephalon, which is part of the limbic system which participates in the subjective central mechanism of the emo-

tions and sexuality.²⁰ Fliess,²¹ an otorhinolaryngologist, who was a disciple of Freud, wrote in 1895 *Les relations entre le nez et les organes génitaux féminins (The Relationship Between the Nose and the Female Sexual Organs)*.

In the allergy literature, the first allergic reaction involving the genital tract of women was described by Cook in 1922.⁴ Later, some authors described the association between rhinitis and vaginitis caused by pollen.^{3,4,8,22} Recently, Moraes⁹ described the association between rhinitis and vaginitis caused by house dust mites in a child. Asthma is not mentioned in these reports.

In 1951 Keeney first reported asthma due to the yeast form of *C. albicans*.²³ In 1956, Itkin and Dennis²⁴ performed a provocation inhalation test with an extract of the yeast, in which they proved a causal relationship between the yeast and allergy. In both studies, an immediate response to *Candida* was present in the skin of the patients. Akiyama et al^{16,25} and Gumowski et al²⁶ reported positive correlations between results of skin and provocation tests and RAST with patients' histories of asthma due to *Candida*.

In the 1970s, Kuldelko,⁵ Palacios,⁶ and Rosedale and Browne²⁷ reported many cases of women with recurrent vaginal candidiasis who showed immediate skin test positive reactions to inhalants and *C. albicans*. The majority of these referral cases also showed rhinitis, family history of allergy, and clinical improvement with specific immunotherapy. All of them were adult women, a fact that is easily explained because *Candida* needs an estrogenic vagina to develop.¹¹

Finally, Witkin et al⁷ identified *Candida*-specific IgE in vaginal washes of women with recurrent vaginal candidiasis. These antibodies were not found in blood, suggesting a local immediate hypersensitivity. In the same study, vaginal IgE against semen and pollen were identified too.

In 1990, Rigg et al² reported 70% of atopy in patients with recurrent vaginal

candidiasis referred by gynecologists. There was approximately 79% improvement with allergy immunotherapy using *Candida* extract. In 1994, Régulez et al²⁸ identified IgE anti-*C. albicans* in patients with acute vulvovaginal candidiasis. In 1996, Moraes²⁹ also reported an association with allergic rhinitis and an improvement of 70% after immunotherapy in patients with chronic candidiasis referred by gynecologists.

The present study has two main findings. First, recurrent vaginal candidiasis is statistically associated with allergic rhinitis and this specific association cannot be explained. Second, the majority of patients are atopic. These findings are in accordance with the results of the majority of previously published studies, which indicate that, in a subpopulation of patients, recurrent candidiasis may have an allergic etiology. It suggests that many women suffering chronically from this tragic disease may find relief after an accurate allergic evaluation.

In conclusion, further research is necessary to define the role of allergy and other suspected risk factors in the pathogeny of *C. albicans* infection. To understand the underlying mechanisms of the disease and its association with allergic rhinitis, future investigations should study the natural history of the disease. Although recurrent vaginal candidiasis is never fatal, this disease causes a great amount of suffering to many women. Research of new drugs is not enough. Future epidemiologic studies should focus on risk factors that could be preventable, thereby contributing to better management of the problem by future generations.

ACKNOWLEDGMENTS

I would like to thank Dr Eugênio Goulart from Universidade Federal de Minas Gerais, for the statistical analysis and consultation on epidemiology, Dr Nelson Mendes from Escola Paulista de Medicina for his encouragement and suggestions, Mr Mark Henry and Mrs Judy Robbe for proofreading the paper.

REFERENCES

1. Working Group of the British Society for Medical Mycology. Management of genital candidiasis. *Br Med J* 1995; 310:1241-48.
2. Rigg D, Miller M, Metzger J. Recurrent allergic vulvovaginitis: treatment with *Candida albicans* allergen immunotherapy. *Am J Obst Gynecol* 1990; 162:332-6.
3. Mitchell WV, Sivon I, Mitchel TH. Vulvovaginal pruritus associated with hay fever. *Ann Allergy* 1948;6:144-5.
4. Berman B. Seasonal allergic vulvovaginitis caused by pollen. *Ann Allergy* 1964;22:594-7.
5. Kuldelko N. Allergy in chronic monilial vaginitis. *Ann Allergy* 1971;29: 266-7.
6. Palacios H. Hypersensitivity as a course of dermatologic and vaginal monilias resistant to typical therapy. *Ann Allergy* 1976;37:110-13.
7. Witkin SS, Jeremias J, Ledger WJ. A localized vaginal allergic response in women with recurrent vaginitis. *J Allergy Clin Immunol* 1988;81:412-6.
8. Dhaliwal A, Fink JN. Vaginal itching as a manifestation of seasonal allergic disease. *J Allergy Clin Immunol* 1995; 95:781-2.
9. Moraes PSA. Allergic vulvovaginitis induced by house dust mite. *J Allergy Clin Immunol* 1998;101:557-558.
10. Dean AD, Dean JA, Burton AH, et al. Epi Info, Version 5.01: a word processing, database and statistics program for epidemiology on microcomputers. USD, Incorporated, Stone Mountain, Georgia, 1991.
11. Michel R, Mycocos. In: Mandell D & Bennett, eds. Principles and practice of infectious diseases, fourth edition, New York: Churchill Livingstone, 1995:2289-96.
12. Bishop MP, Merkus JM. Co-treatment of the male partner in vaginal candidiasis: a double-blind randomized control study. *Br J Obstet Gynaecol* 1986;93:79-81.
13. Edge G, Pepys J. RAST test avec des antigenes protéiniques et polysaccharidiques de les cellules lavées. *Rev Franç Allergol* 1976;16:251-5.
14. Savolainen J, Viander M, Koivikko A. IgE, IgA, and IgG antibody response to carbohydrate and protein antigens of *Candida albicans* in asthmatic children. *Allergy* 1990;45:47-53.

-
15. Anderson JA, Chai H, Clemon HN. Candidiasis hypersensitivity syndrome (position statement). *J Allergy Clin Immunol* 1986;78:271-3.
 16. Akyiama K, Shida T, Yasueda H, et al. Atopic asthma caused by *Candida albicans* acid protease: case reports. *Allergy* 1994;49:778-81.
 17. Savolainen J, Lammintausta K, Kalimos K, et al. *Candida albicans* and atopic dermatitis. *Clin Exp Allergy* 1993;23:332-9.
 18. Girard JP. Les levures opportunistes. Repenser le rôle de *Candida albicans*. *Med Hyg* 1985;43:2711-3.
 19. Armengot M, Marco M, Ruiz M, et al. Hormonas e mucosa nasal. Una revisión bibliográfica. *Anales O.R.L.Iber.-Amer* 1990;17(3):317-28.
 20. Machado A. Áreas Encefálicas Relacionadas com as Emoções. O Sistema Límbico. In: Machado A, ed. *Neuroanatomia Funcional*. 2 edição. Belo Horizonte: Livraria Atheneu Editora, 1993:277-81.
 21. Masson, Jeffrey. *The complete letters of Sigmund Freud to Wilhelm Fliess*. Boston, Massachusetts: The Belknap Press of Harvard University, 1985: 55-8.
 22. Mulligan RM. Pollinosis with intense pruritus vulva. *Ann Allergy* 1951;9: 104-5.
 23. Keeney IEL. *Candida* asthma. *Ann Allergy* 1951;34:223-9.
 24. Itkin IH, Dennis M. Bronchial hypersensitivity to extract of *Candida albicans*. *Allergy* 1956;37:187-95.
 25. Akyiama K, Yni Y, Shida T. Relationship between the results of skin, conjunctival and bronchial tests and RAST with *Candida albicans* in patients with asthma. *Clin Allergy* 1981;11:343-53.
 26. Gumowski P, Lech B, Chaves I, et al. Chronic asthma and rhinitis due to *Candida albicans*, epidermophyton, and trichophyton. *Ann Allergy* 1987; 59:48-51.
 27. Rosedale N, Browne K. Hyposensitization in management of recurring vaginal candidiasis. *Ann Allergy* 1979; 43:250-3.
 28. Regúlez P, Fernandes JF, Moragues MD, et al. Detection of anti-*Candida albicans* IgE antibodies in vaginal washes from patients with acute vulvovaginitis candidiasis. *Gynecol Obstet Invest* 1994;37:110-4.
 29. Moraes PSA. Immunotherapy in recurrent vaginal candidiasis—a prospective study of 36 patients. *J Bras Ginec* 1996;106(5):155-9.
- Requests for reprints should be addressed to:*
Paula S A Moraes, MD
Rua Felipe dos Santos
204/801
MG Brazil
CEP 30-180-160
-