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Invited Article

Candida Vulvovaginitis

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=Abstract=

Candida vulvovaginitis is caused by *Candida albicans* or, occasionally, by other *Candida* species, *Toruopsis* species (also known as *Candida glabrata*), or other yeasts. An estimated 75% of women have at least one episode of *Candida* vulvovaginitis, and 40~45% have two or more episodes. A small percentage of women (less than 5%) experience recurrence. Typical symptoms of *Candida* vulvovaginitis include pruritus and vaginal discharge. Other symptoms may include vaginal soreness, vulvar burning, dyspareunia, and external dysuria. *Candida* vulvovaginitis is often associated with the use of broad-spectrum antibiotics, pregnancy, low vaginal pH, and diabetes mellitus. Sexual activity and oral contraception may also be contributing factors. In healthy individuals, *Candida* species usually remain superficial and respond readily to treatment. The infection by these species depends upon the immune status, as well as the normal vaginal flora status, of the potential host. **[Kor J Med Mycol 4(2): 91-97]**

Key Words: *Candida*, Vulvovaginitis, Epidemiology, Pathogenesis

INTRODUCTION

Vulvovaginitis is one of the most common fungal diseases in the United States and in the United Kingdom. The most frequently encountered cause of this condition is the yeast *Candida albicans*. While there are no reliable figures defining the incidence of vulvaginitis in Asian countries, statistical data in China derived from patients whose condition was diagnosed as *Candida* infections show a sharp increase during the last decades[1]. Most *Candida* infections are accompanied by genital pruritus, so called "feminine itch." The normal vaginal flora constitutes an important local defense mechanism against *Candida* infection. In addition, the host immune system also play its role against *Candida* present locally in vulvo-vaginal tissue. When these normal defense mechanisms are disturbed or become defective, the resulting environment may provide *Candida* with its opportunity to act as a pathogen and cause infection. The incidence, species, epidemiology, pathophysiology, predisposing factors, symptoms, diagnosis, and recurrence of the *Candida* vulvovaginitis are reviewed.

INCIDENCE AND SPECIES

Vulvovaginitis, an inflammation of the vulva and vaginal tissues, is the most common clinical manifestation of fungal infections causing human mycoses; the incidence occurs in 10% of women, during pregnancy the incidence achieves 30% of cases[2]. *Candida* appears to be the species recovered in as many as 90% of clinical vaginal "yeast infections." It is estimated

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that 75% of women experience at least one episode of *Candida* vulvovaginitis during their lifetime, and 40% to 45% experience two or more episodes; a small percentage of women (probably <5%) experience recurrent infection[3,4]. The incidence of *Candida* vulvovaginitis is most common in the late luteal phase just before menstruation[5]. In contrast to the highly frequent occurrence of *Candida* vulvovaginitis in the adolescent and reproductive years, candidal infections in a prepubertal girl is uncommon, except those who have been on antibiotics[6,7].

While other yeasts may occasionally cause clinical infection, *Candida albicans* is the organism isolated from most patients. Approximately 90% of yeast isolated from the vagina are *Candida albicans* strains[8,9]. The rest are due to non-albicans *Candida* species, the most common of which are *Toruopsis glabrata* (also known as *Candida glabrata*). Recently, the prevalence of *Candida* vulvovaginitis caused by non-albicans species (*C. glabrata and C. tropicalis*) has increased in the setting of a vaginitis clinic; 10% in 1988 to 17% in 1995[10]. In particular, vaginal *Candida glabrata* infections have increased significantly and are particularly common in women with uncontrolled diabetes mellitus[11]. Recurrent vaginal candidiasis is another risk factor for vaginitis caused by non-albicans species[10]. Previous antimycotic therapies in susceptible individuals could cause a selection of non-albicans species, especially *T. glabrata*, which is occasionally resistant to the commonly used antimycotic drugs. Isolation of *Saccharomyces cerevisiae* from the vagina of symptomatic patients should not be ignored since treatment of vaginal infection with this yeast requires selected, often prolonged therapy. However, vaginitis due to *Saccharomyces* species is extremely rare[12].

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Candida has been isolated from the mouth, intestine, skin, and vagina of asymptomatic patients. Biotyping of *Candida albicans* strains has been clinically useful in fingerprinting individual strains[13,14]. Although more than 350 strains of *Candida albicans* have been identified, there is no evidence of strain tropism. Thus, all strains appear capable of colonization and cause vaginitis. However, adherence is considered to be an important attribute of vulva-vagina ecology and is a determinant of infectious disease. *Candida albicans* adheres in significantly higher numbers to vulvo-vaginal epithelial cells than do non-albicans *Candida* species and other pathogenic species such as *Staphylococus aureus*[8,15]. This may explain the relative high frequency of the *Candidia albicans* species in vaginitis. In addition, *Candida albicans* possesses the ability to switch reversibly and at high frequency between a number of heritable phenotypes distinguishable by colony morphology and in some cases cellular phenotype[16]. Switching may contribute to the pathogenesis of *Candida albicans* by providing it with the capacity to invade diverse sites in the body, to change resistance to antifungal agents, or to change antigenicity. The molecular basis of switching is probably due to the reversible transposition or rearrangement of genomic elements.

Candida vulvovaginitis usually is not sexually acquired or transmitted. Sexual activity may be more contributory to the production of clinical disease (causing mild abrasions) than simple transmission of the organism. Higher incidence of candidiasis is noted in the summer months. The excess moisture may upset the balance of microbes and allow an overgrowth of *Candida*. In most patients, these infections are flare up and then heal. However, patients with weak immune systems, this yeast can cause more serious or chronic *Candida* vulvovaginitis.

A number of different factors have been found to influence the *Candida* infection of the vagina. Studies showing an increased rate of colonization associated with pregnancy, menstruation, oral contraceptive use, and estrogen replacement the-

rapy illustrate the influence of hormones, glycogen content, and pH on vaginal colonization of *Candida* species. Vaginal colonization of *Candida* species appears to be altered in patients with diabetes mellitus, those receiving steroid therapy, and immunosuppressed individuals.

Candida exists in two morphogenetic forms; cellular (spores) and mycelial (hyphae). When *Candida* is in the actively growing phase (mycelial state), it is considered pathogenic. Vaginal candidiasis usually begins with the adherence of *Candida* cells to the vagina epithelium and changes to the mycelial form. This is believed to be followed by a release of a cellular toxin or a protease enzyme leading to extensive damage of normal cells and resulting in the symptoms of vaginal candidiasis.

The role of candidal proteolytic enzymes, toxins, and phospholipase in determining the virulence of the organism has not clearly been defined. However, several clinical and experimental evidence support a role for secretory proteinase as a virulence factor in the pathogenesis of *Candida* vulvovaginitis. Experimental vaginal infection was significantly more extensive and persistent in rats infected with the proteinase-producer strain than in those challenged with the proteinase-deficient mutant, and the enzyme was detected in the vaginas of the former but not of the latter animals[17]. The presence of the secretory aspartate (acid) proteinase has been confirmed in the vaginal fluid of candidal vaginitis patients, when studies were conducted with ELISA and immunoblot (Western blot). Also, worth attention are results regarding symptomic candidiasis of vagina and enzymatic properties of *Candida albicans*. Krzeminska-Jaskowiak and colleagues found that, among 145 strains of *Candida albicans* isolated from cases of symptomatic *Candida* vulvovaginitis, 67 exhibited both lipolytic and proteolytic activities. At the same time, in asymptomatic *Candida* vulvovaginitis only 14 strains of *Candida albicans* exhibited same properties[18].

PREDISPOSING FACTORS

A number of factors are known to predispose to *Candida* vulvovaginitis. Physiological variations such as pregnancy are well recognized to predispose to the condition of a higher incidence of colonization and symptomatic *Candida* vulvovaginitis. During pregnancy, the higher levels of reproductive hormons provide a higher glycogen content in the vaginal environment, which is an excellent carbon source for *Candida* to grow. These hormones also enhance yeast mycelial formation. High-estrogen oral contraceptives are believed to be associated with an increased incidence of candidosis. Low-estrogen oral contraceptives are not believed to cause vaginal candidiasis, possibly due to the lack of or decreased amounts of estrogen. However, use of low-dose oral contraceptives may be a risk factor for recurrent candidiasis because of their effect on the hormonal environment.

Symptomatic *Candida* vulvovaginitis is frequently observed during or after courses of systemic antibiotics. In particular, the broad-spectrum antibiotics are considered to be mainly responsible for the exacerbation. Antibiotics, both systemic and topical agents, are thought to act by eliminating the normal protective vaginal bacterial flora. The natural flora are thought to provide a colonization-resistance mechanism and prevent candidal germination and superficial mucosal invasion. In particular, aerobic and anaerobic Lactobacillus species have been cited as providing this protective function. Current concepts of the Lactobacillus-*Candida* interaction include competition for nutrients and steric interference by lactobacilli of candidal adherence to vaginal epithelial cells. In addition, women with recurrent bacterial vaginosis are also at increased risk for acquiring *Candida* superinfection. The recurrent bacterial vaginosis is characterized by a polymicrobial condition in which a decrease in vaginal acidity and in the concentration of lactobacilli is accompanied by an increase of a

100-fold or more in the concentration of other organisms. Vulvovaginal candidiasis has been reported in 40% of patients with this recurrent bacterial vaginosis; 1/3 of patients had concurrent infections.

Candida vulvovaginitis is common in diabetic women, presumably because traces of sugar-laden urine around the introitus offer a suitable culture medium for the yeasts. Studies find vaginal yeast infections in over one third of a diabetic women. Hypothyroidism, hypoparathyroidism and Addison's disease have all been found to be associated with recurrent candidiasis. Other medical conditions such as iron deficiency states, severe malnutrition and possibly immunodeficiency may be associated with recurrent candidiasis. Intravaginal trauma (eg, microscopic abrasions) associated with sexual activity; also may be a risk factor for recurrent candidiasis. There is a miscellany of other possible associated factors such as oral sex, local allergy, low vaginal pH, and so on, which may all have a part to play. However, in the majority of cases no predisposing factor is apparent and thus *Candida* vulvovaginitis remains as a relative enigma.

SYMPTOMS AND DIAGNOSIS

Typical symptoms of *Candida* vulvovaginitis include pruritus (vulvovaginal itching and irritation) and vaginal discharge[19,20,21]. Other symptoms may include vaginal soreness, vulvar burning, dyspareunia, and external dysuria. As the disease progresses, burning, soreness, and pain with urination (vulvar or external dysuria) or wiping occurs. Vaginal discharge is a frequent but not universal complaint. Dyspareunia or dysuria may be reported. Erythema, excoriation (from scratching), and small red satellite lesions may be present. Vaginal secretions may range from scanty discharge to thick, white, and curdy; the classic "cottage-cheese" discharge occurs only in a minority of patients. Symptoms and signs tends to be more severe in women with higher yeast counts ($>10^3$ colony forming units/ml)[22].

The diagnosis of *Candida* vulvovaginitis should not be made based on symptoms alone. Clinical correlations between laboratory findings and the woman's condition are essential to diagnose vulvo-vaginal candidiasis accurately. The diagnosis can be made when a woman has signs and symptoms of vaginitis, and when a wet preparation of Gram stain of vaginal discharge demonstrates yeasts or pseudohyphae, or when a culture or other test yields a positive result for a yeast species. Vaginitis solely because of *Candida* infection is associated with a normal vaginal pH (<4.5).

Use of potassium hydroxide (KOH) in wet preparations improves the visualization of yeast and mycelia by disrupting cellular material that may obscure the yeast or pseudohyphae. Identifying *Candida* in the absence of symptoms should not lead to treatment, because approximately 10% to 20% of women normally harbor *Candida* species and other yeasts in the vagina. Vulvo-vaginal candidaisis may be present concurrently with sexually transmitted diseases.

RECURRENCE

A subgroup of women develop chronic or recurrent symptomatic vulvo-vaginal candidiasis. The reasons for this remain uncertain. One hypothesis is that the frequent episodes might be due to reinfection of vagina from a persistent intestinal source or as a results of sexual transmission. The intestinal reservoir hypothesis is based on the report that *Candida* species could be cultured from rectal swabs in most women with recurrent vulvo-vaginal candidiasis. However, this hypothesis has been refuted by the demonstration of much lower concordance between rectal and vaginal cultures. Furthermore, some women have persistent intestinal yeast carriage without vaginal colonization. Penile colonization with *Candida* species is found in approximately 20% of male partners of infected women and strain-typing techniques have indi-

cated that infected partners usually carry the same strain. However, the confirmation that sexual transmission occurs is still lacking, and the contribution of sexual transmission to the pathogenesis of infection is unknown currently. The clinical evidence to date has not demonstrated any prevention or reduction of recurrent attacks in the female by antifungal treatment of the male partner. Reinfection from the lower gastrointestinal tract or by sexual partners is a possible source of recurrent vulvo-vaginal candidiasis, but is not considered to be a major cause of recurrent vulvo-vaginal candidiasis.

Relapse is another possible cause of recurrent vulvo-vaginal candidiasis. A theory that recurrent vulvo-vaginal candidiasis is caused by the persistence of a single yeast genotype that undergoes morphological and behavioral changes in the presence of antifungal agents due to the selective pressure to which it is submitted. Topical antifungal therapy may decrease the numbers of viable yeasts in the vulvo-vaginal surface area, but *Candida* can persist in deeper tissue layers because of the invasive nature of this species. When conditions are favorable, the yeast can begin to grow again and recolonise the vulvo-vaginal surface, initiating another attack. However, episodes of recurrent vulvo-vaginal candidiasis is not attributable to antifungal resistance. Strain-typing methods show that in more than 66% of recurrent suffers identical strains are found at each episode. Furthermore, negative cultures appear to become positive within 4～6 weeks of completion of therapy in approximately 20～25% of women. These observations support a relapse theory.

Separately, host immunity plays an important role in protecting against vulvo-vaginal candidiasis. Studies have demonstrated that in some women susceptible to recurrent vulvo-vaginal candidiasis, exposure to *Candida* antigen can induce an increased production of prostaglandin E_2 by macrophages. Prostaglandin E_2 acts to inhibit the production of the cytokine interleukin-2, which regulates normal T-lymphocyte proliferation. This leads to a decrease in anti-candidal T-lymphocyte proliferation and a consequent decrease in cell-mediated immunity. This decrease in locally acquired mucosal immunity, distinct from that in the peripheral circulation, serves to increase the host susceptibility to candidal infection and therefore to symptoms. Changes in local cell-mediated immunity may predispose to recurrent vulvo-vaginal candidiasis.

TREATMENT

Treatment of *Candida* vulvovaginitits is considered to be quite simple and efficient except in a small group of women who are prone to recurrent *Candida* infections. Antifungal agents are available for local use as creams, lotions, vaginal tablets, suppositories, and coated tampons.

Nystatin (polyene) and imidazole derivatives have been widely used as topical agents for acute *Candida* vulvovaginitis. The various azole derivatives (85～90%) achieve slightly higher clinical and mycologic cure rates than the polyenes (75～80%)[8,23]. The duration of treatment is shorter with the imidazole derivatives, compared to that of the polyene group that requires 14 days to be effective.

Ketoconazole (400 mg daily for 5 days), itracozole (200 mg daily for 3 days or 400 mg for 1 day), fluconazole (150 mg for 1 day), and other imidazole group, as oral systemic agents, have been shown to be highly effective as oral systemic antimycotic agents, in particular, for *Candida* vulvovaginitis. Ketoconazole therapy is accompanied by a small incidence of side effects including headache, hepatotoxicity[24], and rare anaphylaxis[25]. Similar side effects appear to be much less frequent with itraconazole and fluconazole.

Treatment of recurrent and chronic *Candida* vulvovaginitits requires a long-term maintenance prophylactic regimen (e.g., 100 mg ketoconazole daily for 6 months). Prior to the treatment, however, the clinician should confirm the diag-

nosis of *Candida* vulvovaginitits. For women in whom antibiotics have been identified as a precipitating factor, the recurrent and chronic *Candida* vulvovaginitits treatment requires antimycotic therapy simultaneously with antibiotic agents.

CONCLUSION

Our understanding about pathogenesis, diagnosis, and treatment of *Candida* vulvovaginitis has significantly increased during the last several decades. Due to the presence of various predisposing factors recurrence is still a major problem. However, it becomes apparent that an impaired immunity to *Candida* may contribute significantly to the pathogenesis of vulvovaginal candidiasis.

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