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Rapid Communication

Exploring the New Targets for Candida Vaginiitis

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A vaginal yeast infection, also known as vaginal candidiasis, genital candidiasis, or Vulvovaginal Candidiasis (VVC), is an infection involving a type of fungus, or yeast. The fungus most commonly associated with vaginal yeast infection is called *Candida albicans*, which account for up to 92% of all cases, with the remainder due to other species of *Candida*. These fungi can be found all over the body and are normally present in warm and moist areas of the body. Studies have shown that up to 20%-50% of all women normally carry yeast in the vagina without the presence of symptoms. When *C albicans* in the vagina multiplies to the point of infection, this infection can cause vaginal inflammation, irritation, odor, discharge, and itching.

The vagina creates its own environment and maintains a balance among the normal bacteria found there and the hormonal changes in a woman's body. Vaginitis occurs when the vaginal ecosystem has been changed by certain medications such as antibiotics, hormones, contraceptive preparations (oral and topical), douches, vaginal medication, sexual intercourse, sexually transmitted diseases, stress, and change in sexual partners.

Some vaginal infections are transmitted through sexual contact, but others such as yeast infections probably are not. Vaginitis means inflammation and is often caused by infections, but may be due to hormonal changes (especially when a woman is going through menopause) or due to trauma in young girls. Some infections are associated with more serious diseases.

Three vaginal infections are the most common. Their causes are quite different but, their signs and symptoms are similar, and treatments of the three conditions vary.

1. *Bacterial vaginosis*
2. *Vaginal yeast infection*
3. *Trichomoniasis*

Bacterial Vaginosis (BV) causes an abnormal vaginal discharge with an unpleasant odor. Some women report a strong fishlike smell, especially after intercourse. The discharge is usually white or gray, and it can be thin. You may also have burning during urination or itching around the outside of the vagina, or both. Some women with bacterial vaginosis have no symptoms at all.

Yeast infections or candidiasis cause a thick, whitish-gray "cottage cheese" type of vaginal discharge and may be itchy. You may have intense itching in your genital area. Painful urination and intercourse are common. You may not always have a vaginal discharge. Men with genital candidiasis may have an itchy rash on the penis. Most male partners of women with yeast infection do not experience any symptoms of the infection.

Trichomoniasis causes a frothy vaginal discharge that may be yellow-green or gray, itching and irritation of the genitals,

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burning with urination (sometimes confused with a urinary tract infection), discomfort during intercourse, and a foul smell. Because trichomoniasis is a sexually-transmitted disease, symptoms may appear within 4-20 days after exposure. Men rarely have symptoms, but if they do, they may have a thin, whitish discharge from the penis and painful or difficult urination.

A yeast infection results from an overgrowth of yeast (a type of fungus) anywhere in the body. Candidiasis is by far the most common type of yeast infection. There are more than 20 species of *Candida*, the most common being *Candida albicans*. These fungi live on all surfaces of our bodies. Under certain conditions, they can become so numerous they cause infections, particularly in warm and moist areas. Examples of such infections are vaginal yeast infections, thrush (infection of tissues of the oral cavity), skin and diaper rash, and nailbed infections.

Available Medication

- Miconazole (Micon 7, Monistat 3, Monistat 5, Monistat 7, M-Zole Dual Pack)
- Tioconazole (Monistat-1, Vagistat-1)
- Butoconazole (Gynazole 1)
- Clotrimazole (Femcare, Gyne-Lotrimin, Mycelex-G)

Candida organisms are dimorphic, and may be found in humans during different phenotypic phases. In general, blastospores represent the phenotype responsible for transmission or spread of *Candida,* and are associated with asymptomatic colonization of the vagina. In contrast, germinated yeast producing mycelia most commonly constitute a tissue-invasive form of *Candida,* usually identified by the presence of symptomatic disease along with larger numbers of blastospores.

In earlier epidemiologic studies directed at identifying strains with specific tropism for the vagina, no such tropism was identified [1]. Similarly, no evidence emerged of vaginopathic strains of *C. albicans* demonstrating greater or lesser virulence. This might explain why some women remain heavily colonized with *Candida* spp., despite being entirely asymptomatic, whereas other women develop severe symptomatic vaginitis. DNA typing has provided a more reliable and easily reproducible method of answering these questions. Using computer-assisted DNA-probe typing, Soll and co-workers [2] have presented data to support the concept of "vaginal tropism", in which *Candida* selected organisms demonstrate adaptation to unique anatomic niches that facilitate persistence and survival at certain anatomic sites, including the vagina.

In order for species of *Candida* to colonize the vagina, they must first adhere to vaginal epithelial cells. *Candida albicans* adheres to such cells in numbers significantly higher than those of *C. tropicalis, C. krusei, and C. kefyr* [3]. *This* may explain the relative infrequency of the latter species causing vaginitis. All *C. albicans* strains appear to adhere equally well to exfoliated vaginal and buccal epithelial cells. The ready availability of erythrocytes and hemoglobin in the vagina creates an ideal niche for yeast possessing erythrocyte-binding surface receptors.

Candida organisms gain access to the vaginal lumen and secretions predominantly from the adjacent perianal area [4]. Age appears to be an important factor in the overall incidence of vulvovaginal candidiasis which is seen predominantly in women of child bearing age. While the condition is extremely rare prior to menarche, the annual incidence increases dramatically toward the end of the second decade of life and peaks over the next two decades. Among college women, CV is more common among black than among white women [5] and is associated with the initiation of sexual activity [6]. High estrogen levels apparently favor overgrowth of yeasts, although such levels also promote the growth of lactobacilli [7,8]. CV is more common in pregnancy and occurs in 10% of first trimester women and in 36% to 55% of women in their third trimesters [9]. Symptomatic disease has eventually developed in 60% to 90% of pregnant carriers, and old inoculation studies have confirmed the increased susceptibility of pregnant [9]. High levels of reproductive hormones provide an excellent carbon source for Candida organisms by producing higher glycogen content in the vaginal tissue [10]. A more complex mechanism is likely, in that estrogen enhances adherence of yeast cells to the vaginal mucosa.

The onset of symptomatic CV is frequently observed during courses of systemic topical antibiotics. Broad-spectrum antibiotics, such as tetracycline and beta-lactams, are mainly responsible for exacerbation of symptoms [11]. Vaginal colonization rates increase from approximately 10% to 30% [12]. Antibiotics are thought to facilitate CV by eliminating the protective vaginal bacterial flora. Natural flora is thought to provide colonization resistance as well as to prevent germination and hence superficial mucosal invasion. In particular, aerobic and anaerobic resident lactobacilli have been pinpointed as providers of this protective function. Low numbers of lactobacilli in vaginal cultures were observed in women with symptomatic CV [13]. The current concept of lactobacilli-yeast cell interaction includes competition for nutrients, and lactobacilli's steric interference of receptor sites on vaginal epithelial cells for *Candida* organisms [14].

The incidence of CV increases dramatically in the second decade of life, corresponding with the onset of sexual activity. It peaks in the third and fourth decades then declines in females older than 40 years. Sexual transmission of CV occurs during vaginal intercourse, although the relative role of sexual and nonsexual practices in introducing CV into the lower genital region has not been [1,15,16]. The likelihood that sexual behavior may play a role in CV is logical, but epidemiological evidence is limited [17]. The source of *Candidal* infection for vaginal colonization may be initiated by the gastrointestinal tract, although this remains highly controversial [18]. Species of *Candida* were recovered on rectal cultures from 100% of women with recurrent CV. Furthermore, the majority of *Candida* strains isolated from the rectum and the vagina are identical [18]. However, women prone to recurrent CV are not known to suffer from perianal or rectal candidiasis. Two controlled studies using oral nystatin treatment, which reduces intestinal yeast carriage, failed to prevent symptomatic recurrence of CV [18,19]. With respect to sexual transmission, penile colonization with *Candida* organisms is present in approximately 20% of male partners of women with recurrent CV [15,16]. Asymptomatic male genital colonization with species of *Candida* is four times more common in male sexual partners of infected women and infected partners usually carry identical strains [1,15]. Despite the aforementioned evidence indicating that sexual transmission does occur, the contribution of sexual transmission to the pathogenesis of infection remains unknown. The lack of specificity of symptoms and signs of CV precludes a diagnosis that is based soley on history and physical examination. Clinical signs and symptoms alone also should not be regarded as a satisfactory basis for diagnosis. Regrettably, both approaches are common in practice, as a myriad of infections and non-infections may cause patients

to present identical signs and symptoms, hence the need for laboratory confirmation. Bergman and colleagues emphasized that a patient's symptoms are of little practical value in predicting CV [20]. The most specific symptom in genital *Candida* infection is pruritus without discharge, and even this criterion correctly predicted CV in only 38% of patients [20]. At present, laboratory identification of *Candida* species requires culturing and other microscopic preparation techniques, which are time-consuming and have an inherent weakness in that they may not be species-specific. Further complicating traditional analysis is the increasing number of auxotrophs that do not grow on the media required to perform the tests [21]. Diagnosis of *C. glabrata* vaginitis is more difficult than that of typical *Candida* vaginitis because of the failure of this organism to form pseudohyphae and hyphea *in vivo*. Accordingly, on saline and KOH microscopy, numerous budding yeasts are seen, but hypha elements are absent. There is some evidence that vaginitis with *C. glabrata* often occurs at a somewhat higher vaginal pH, usually at the upper limit of normal. Not infrequently, *C. glabrata* vaginitis co-exists with bacterial vaginosis, and the higher pH of the latter may represent the link between the two entities.

The incidence of *Candida Vaginitis* (CV) is poorly documented, particularly since CV is not a reportable entity. Regrettably, CV is routinely diagnosed without laboratory testing, resulting in as much as 50% misdiagnosis [22]. Data on incidences where diagnostic data were based on definite clinical and mycologic findings are exceptional. Moreover, most studies have been carried out in Sexually Transmitted Disease (STD) clinics and family planning or student health clinics which largely ignore older women and those in the private sector. Most studies suggest a CV prevalence of 5% to 15%, depending on the population studied [23]. CV affects most females at least once during their lives, at an estimated rate of 70% to 75%, of whom 40% to 50% will experience a recurrence [6,5]. Statistical data from England have shown a sharp increase in the annual incidence of CV, from 118 per 100,000 women to 200 per 100,000 women during the last 20 years (Annual reports of chief medical officer, 1976-1984). In the United States, CV is currently the second most common cause of vaginal infections, with bacterial vaginosis as the most common diagnostic entity [24]. Based on a number of prescriptions written to treat yeast infections between 1980 and 1990, the incidence of CV almost doubled and these cases numbered approximately 13 million in 1990. Point-prevalence studies indicate that *Candida* spp. may be isolated from the lower genital tracts of approximately 20% of asymptomatic healthy women without abnormal vaginal discharge [25]. Among women with symptoms of vulvoginitis, 30% had yeast isolated, confirming the diagnosis of CV [26]. Most studies indicate that CV is a frequent diagnosis among young women, affecting as many as 15% to 30% of symptomatic women visiting a clinician. Half of all college women will have experienced at least one episode of CV by the age of 25 [6].

Acute pruritus and vaginal discharge are the usual presenting complaints, but neither symptom is specific to CV and neither is invariably associated with disease. The most frequent symptom is that of vulvar pruritus. Vaginal discharge is frequently minimal. Although described as typically cottage cheese like in character, the discharge may vary from watery to homogeneously thick. Vaginal soreness, irritation, vulvar burning, dyspareunia, and external dysurea are commonly present. Odor, if present, is minimal and no offensive. Examination frequently reveals erythema and swelling of the labia and vulva, often with discrete pustulopapular peripheral lesions and fissure formation. Certain predisposing factors associated with increased yeast growth include glycosuria, diabetes mellitus, pregnancy, obesity, and recurrent use of antibiotics, steroids or immunosuppressive agents.

In men, *Candida* infection is expressed as a transient rash, erythema, and pruritus or a burning sensation of the penis that develops minutes after unprotected intercourse. The symptoms are self- limited and frequently disappear after showering.

In view of the above-mentioned status of the research work ongoing in India and elsewhere, it is quite clear that *Candida* viginitis has been neglected and no solid study has been reported on the same so far. We therefore propose the following grounds.

The identification of specific markers would be achieved which play a major role in *Candida albicans* virulence and *Candida* viginitis disease symptoms presentation. The protein profile changes are the first indications of the kind of immune response that is triggered by the fungal infection and it needs to be obtained in order to have a clear picture of the fungal pathogenesis. Experiments need to be conducted to test which of the fungal features might be responsible for the apparent increase in *Candida*'s ability to infect humans and cause disease. Further, it is very important to note the changes associated with the vaginal epithelium. Since there are only few countable medications available against *Candida* vaginitis, identification of molecular targets is a thirst area. Molecular docking on the identified targets will help us to understand the conformational changes in the proteins brought about by the drug *Candida*tes, which will help in designing of synthetic ligand molecules specific for the drug targets. The knowledge of this may help in future studies to determine the drug target site against *Candida albicans* infection in host.

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