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Recurrent Vulvo-Vaginal Candidiasis: Diagnostic and Management Challenges in a Developing Country Context

Abstract

Vulvo-vaginal candidiasis (VVC) is a very common cause of vaginal symptoms in women, with at least 75% of them experiencing one episode in their reproductive years, 5-10% of who experience recurrences (RVVC) i.e. ≥ 4 specific episodes within one calendar year. It's associated with significant morbidity, affecting the woman's quality of life as well as sexual function.

The pathogenesis of RVVC remains unresolved to date. Majority of the patients are healthy, immunocompetent and have no discernible predisposing or causative factors. There are controversies regarding the identified risk factors, with some studies showing an association and others not. Diagnosis of RVVC is a challenge since its clinical features are not pathognomonic thereof and current laboratory tests are not capable of discriminating between healthy carrier states and symptomatic infections. Successful treatment may be achieved with oral or topical agents, which are equally effective. However, even long-term therapy does not prevent recurrences. Repeated treatment might select and induce drug resistance and a shift toward more resistant Candida species, as well as lead to non-compliance with treatment.

Although diagnosis and management or RVVC are major challenges globally they are much more so in a developing country context because of various health care delivery related constraints. It is often over-diagnosed or misdiagnosed, leading to inappropriate treatment especially in resource-constrained developing countries.

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Abbreviations: VVC: Vulvovaginal Candidiasis; BV: Bacterial Vaginosis; RVVC: Recurrent Vulvovaginal Candidiasis

Introduction

Vulvovaginal candidiasis (VVC) is a frequent and common distressing disease affecting women of all ages and across social strata globally. It is the second most common cause of vaginal infections after bacterial vaginosis (BV) [1]. Estimates indicate that 70%–75% of women of childbearing age worldwide experience at least one episode during their lifetime, and 5%–10% of women with a primary episode of VVC experience frustrating recurrent infections (RVVC) [2], defined as at least three-four specific episodes within one year [3,4]. VVC is rare before puberty, its incidence increasing dramatically in the second decade of life, coinciding with the onset of sexual activity [5]. About 54.7% of women will experience one episode by age 25 [5]. It is classified as "uncomplicated and complicated", which is now internationally accepted [7,8]. It is also classified as sporadic (acute) and recurrent based on the frequency of the infectious episodes [3]. RVVC is part of the complicated vulvo-vaginal candidiasis (Table 1).

Recurrent vulvovaginal candidiasis (RVVC) is defined as four or more specific episodes of VVC or at least three episodes not related to antibiotic therapy, within twelve calendar months, with at least partial resolution of symptoms between episodes and a positive microscopy or culture on at least two occasions when symptomatic [7,9,10]. There are two forms of RVVC: primary RVVC which is idiopathic with unknown predisposing factors. This occurs in otherwise healthy, immunocompetent women, majority of who have no discernible precipitating or causative factors [11]. Secondary RVVC is the occurrence of frequent episodes of acute VVC because of certain predisposing factors such as hormone replacement therapy or diabetes mellitus [12].

Table 1: Classification of Genital Candidiasis.

Feature	Uncomplicated	Complicated
Severity	Mild or Moderate	Severe
Frequency	Sporadic	Recurrent
Organism	*Candida albicans*	*Candida* spp., except *C. albicans*
Host	Normal	Abnormal, (e.g. uncontrolled diabetes mellitus)

The primary pathology in genital candidiasis is inflammation of the vulva and vagina secondary to an overgrowth of Candida. The resultant symptoms and clinical signs are not only non-specific but also not sensitive, i.e. not pathognomonic for candidiasis [13,14]. Likewise the respective laboratory tests often fail to identify candida infection in symptomatic individuals [3,15]. This is partly because the current laboratory tests are not capable of discriminating between asymptomatic carriers and symptomatic candidiasis and that a good proportion of RVVC is due to non-albicans Candida, the most common being *C. glabrata*, which is

not easily identifiable on microscopy as it does not form hyphae or pseudohyphae [3].

RVVC is often diagnosed and treated on the basis of clinical features, namely symptoms and signs, without confirmatory laboratory tests. Many women self-diagnose and treat with over-the-counter preparations [16]. Since vaginal infections are an extremely common reason for women to seek care from a clinician, VVC is often over-diagnosed or misdiagnosed, leading to inappropriate treatment especially in resource-constrained developing countries. The frequent episodes of vulvo-vaginal candidiasis in RVVC, whose intensity may vary from one episode, or woman to another, lead to significant physical, psychological and social morbidity, as well as marked negative impact on the woman's sexual functioning [3,5].

This paper reviews the pathogenesis, risk factors, diagnosis and management of RVVC with the aim of raising awareness among health care providers in the SSA region. It highlights the challenges in diagnosing and managing RVVC in a developing country context and proposes possible strategies to address them.

Pathogenesis

The pathogenesis of RVVC remains unresolved to date. Candida, the causative organism is a commensal of the human vagina and gut [3], can be isolated from the vaginal tract in 20-30% of healthy, asymptomatic, non-pregnant women at any single point in time and in about 70% of women if followed longitudinally over a one year period [17,18]. *C. albicans* is the most common yeast in both symptomatic and asymptomatic carriers accounting for 80-90% [19,20]. Up to 20% are due to non-albicans, *C. glabrata* being the commonest of them all. Others include *C. tropicalis*, *C. krusei*, *C. parapsilosis* [3,21]. Studies have reported an increased prevalence of non-albicans Candida in RVVC over time [22,23], and studies from developing countries in particular have reported much higher prevalence of non-albicans Candida than the developed. A study in Nigeria by Okungbowa et al. [24] found that non-albicans Candida made up to 80% with *C. glabrata* accounting for 34% [24], while Ahmad et al. [25] in India reported that non-albicans made up 53% of which 37% was due to *C. glabrata* [25].

Local host immune response is crucial in the pathogenesis and host-pathogen interaction in genital candidiasis [26]. Host defense against Candida infection depends on intact mucosal and skin barriers, and adequate recognition of the fungus that subsequently triggers protective innate and adaptive antifungal defense mechanisms [27]. The state of commensalism is said to be temporarily disturbed when Candida causes genital candidiasis (VVC) while in RVVC this balance may be more permanently disturbed. It is still not clear though what causes either this temporary or permanent disturbance! It's been suggested that VVC is associated with signals that promote a non-protective inflammatory leucocyte response leading to the clinical symptoms [1,28]. Alteration of the vaginal ecosystem in certain conditions, which have been identified as risk factors for VVC and RVVC, such as sexual intercourse, use of antibiotics and female hygienic products [29], may also contribute to development of genital candidiasis.

The source of initial Candida involved in vaginal colonization and VVC is thought to be the intestine [8,14]. Recurrent episodes are thought to result from a vaginal relapse following an incomplete clearance of the yeast during a previous episode or vaginal re-infection during sexual intercourse from an intestinal reservoir or the partner's genitalia [3,4,30]. Of these two theories, a vaginal relapse is considered the more plausible because of the short intervals between the episodes as well as the finding that the same Candida species is responsible for the initial and subsequent episodes in the same individual [14,30]. The role of the intestinal reservoir in RVVC has been discounted because attempts to eradicate yeast from the gut have not significantly reduced symptomatic vaginal recurrences [31]. There have been suggestions of possible sexual transmission of Candida in RVVC as male partners of women with RVVC are four times more likely to have asymptomatic colonization of their genitalia with Candida than those of uninfected women [32]. However there is currently no evidence supporting sexual transmission as treatment of male partners does not seem to influence either cure or rate of recurrences [32].

Risk Factors

It's been suggested that women with RVVC are a separate population of otherwise healthy individuals who are distinct from those who experience sporadic or acute VVC. The principal predisposing factors for VVC are the following:

Diabetes mellitus

Vaginal colonization with candida is reportedly more frequent in diabetes than non-diabetic women, those with diabetes mellitus type-2 being more prone to vaginal colonization with non-albicans Candida especially *C. glabrata* [33]. Uncontrolled diabetes mellitus predisposes to symptomatic vaginitis [34].

Immunosuppression

HIV infection is considered one of the risk factors for the development of symptomatic Candida infection. Most studies show a higher prevalence of vaginal candidiasis with a higher recurrence in HIV-infected women than uninfected women [35,36]. In a nested control analysis from a prospective study of 1404 women (716 HIV+ve and 688HIV-ve) in Kwazulu Natal South Africa, Sebitloane et al. [37] showed higher risk among the HIV infected than uninfected (39.2% vs 30.0% RR= 1.31 (1.08 – 1.59) p value = 0.006) [37]. Oliviera et al. [38] found a two-fold increase in the risk among HIV+ve compared to HIV-ve women in Brazil [38]. Some studies have shown that increased rates of colonisation with Candida and symptomatic candidiasis are associated with decreased $CD4^+$ cell count especially below 200 cells/mm^3 [36,39]. HIV+ve women have been shown to have increased rates of colonization with non-albicans Candida more than HIV-ve women [36,40]. Ohmit et al. [41] suggested that mucosal candidiasis in HIV-seropositive women is a consequence of multiple interacting factors [41]. Use of corticosteroids, which may suppress ones immune response, has been reported to increase the risk of symptomatic yeast infection [42,43]. It is worth noting though that majority of women with RVVC are immunocompetent [44].

Contraception

This remains controversial and unresolved. Whereas high-oestrogen contraceptives have been shown to increase the risk of genital candidiasis, [45,46], similar effects have also been shown with low-oestrogen contraceptives [47]**.** Studies have reported an increase in colonization of the vagina in women using the IUCD's, contraceptive sponges, diaphragms and condoms, with or without spermicides [48]**.** However a study involving sexually active college students failed to show increased prevalence of symptomatic candidiasis among those using oral pills, diaphragms, condoms, or spermicides [5].

Pregnancy

The associated high concentration of reproductive hormones especially oestrogen in pregnancy increases the glycogen content in the vaginal epithelial cells, which increases the risk of colonization and symptomatic candidiasis [49,50]. A study by Glover & Larsen [51] among pregnant women showed that vaginal colonization with Candida was a risk factor for subsequent symptomatic candidiasis [51]. RVVC is more common in pregnancy as well as decreased response to antifungal therapy compared to non-pregnant women [52].

Antibiotic therapy

This is an area that has elicited a lot of interest and concerns, cause of the widespread use of antibiotics among women of reproductive years for various ailments. Some studies have shown that VVC frequently follows antibiotic use [19,53,54]. Antibiotics eliminate the protective bacterial flora in the vagina, i.e. lactobacillus, thus allowing overgrowth of yeast [55]. It's been reported that 28-33% of women put on antibiotic therapy develop symptomatic genital candidiasis [54,56]. In a recent study among non-pregnant women receiving antibiotics for non-gynaecological conditions, Xu et al. [57] observed that short courses of oral antibiotics seem to increase the prevalence of asymptomatic vaginal *Candida* colonization and incidence of symptomatic VVC [57]. Their sample size was very small though. Studies have shown that alteration of or abnormal vaginal bacterial flora predispose to RVVC only in the presence of antibiotic use [58,59]. It is worth noting thought that the majority of women who receive antibiotics do not develop genital candidiasis and majority of women with genital candidiasis have not used antibiotics in the immediate past. Glover et al. [60] did not show an association between antibiotic use and VVC or RVVC [60]. Pirotta et al. [54] contend that those who develop genital candidiasis following antibiotic use are already colonized in their vagina by Candida [54]. While that may be true, it does not explain though how antibiotics transform the Candida from a commensal to a pathogen! Their suggestion is not supported by Glover & Larsen [51] who in their study involving a cohort of pregnant women noted that while vaginal colonization is a risk factor for subsequent symptomatic genital candidiasis, antibiotic therapy, even intense therapy thereof, is not associated with an increased risk of developing symptoms [51].

Sexual and behavioural factors

Female genital hygiene habits and practices such as douching, use of deodorants, sprays and medicated soaps on/in the genitalia have been reported to increase the risk of RVVC [61,62]. Likewise wearing of tight-fitting clothes, non-cotton underwears, panty liners and hoses have been reported to increase local genital temperature, humidity and moisture, thus increasing the risk of genital candidiasis [52,62]. Local hypersensitivity or allergic reaction triggered by feminine hygienic practices may predispose some women to colonization with Candida or symptomatic infections [63].

The role of sexual activity per se and various sexual practices in the pathogenesis of genital candidiasis has attracted a lot of interest over the last three decades or so. Calderone et al. [64] opined that the role of sexual behavior in RVVC is underestimated [64]. The possibility of sexual transmission of *Candida* during penile-vaginal intercourse has been based on the fact that male partners of infected women are four times more likely to be colonized by *Candida* on their genitalia than those of uninfected women [65] and 20% of male partners of women with RVVC have *Candida* on their penises [66]. Of course the question would be what came first, i.e. what caused the other! Sexual intercourse alone has not been shown to alter vaginal *Candida* colonization, but certain practices may be of importance for both primary transmission of *Candida* and recurrence of symptomatic episodes (RVVC) [65]. Bailey et al. [67] observed an increased risk amongst women who have sex with women (WSW), which rose with the number of partners [67]. However, in a more recent study, Muznyl et al. [68] did not find evidence supporting sexual transmission of genital *Candida* between women (WSW) [68]. The few studies that have focused on specific sexual practices among women with RVVC have found positive association with early sexual debut, [69], casual sex partners in the preceding month [69], new sex partner in the last six months [70], sex during menses [69], receptive oral and anal intercourse [61,71,72] and frequency of vaginal intercourse [5]. Reed et al. [65] in their study on sexual behavior as a risk factor for RVVC found that female masturbation using saliva and cunnilingus from their partners and male masturbation with saliva increased the risk of genital candidiasis [65].

Genetic factors

Studies have suggested genetic predisposition to RVVC [73,74]. Blood group ABO Lewis non-secretor phenotype has been shown to be associated with increased vaginal colonization with *Candida* and symptomatic candidiasis [22].

Dietary factors

There are suggestions that diets rich in sugar content may increase the risk of genital candidiasis [75,76]. Rylander et al. [72] found an association between consumption of sweets and a positive culture of *Candida* [72]. Patel et al. [52] noted that consumption of cranberry was associated with a ≥2 risk of RVVC [52]. Donders et al. [77] opined that diets rich in refined sugar may increase the risk of genital candidiasis [77]. However other studies did not find evidence to support the role of sugar consumption in genital candidiasis [78]. While deficiencies of minerals such as magnesium, zinc, calcium and iron have been associated with genital candidiasis in some studies, the evidence thereto is considered insufficient [79].

Immunological factors

Despite previous indications that RVVC was associated with systemic immune deficit [80], patients with RVVC are systemically immunocompetent, and that the immune deficit is local [44], i.e. genital. Studies on mouse models and humans highlight the immunopathological response as a crucial element of vaginal candidiasis pathogenesis [81]. It is thought that women with RVVC suffer relapsing genital candidiasis due to a change in the normal host defense mechanisms at the vaginal mucosal level. Mucocutaneous candidiasis is associated with T-cell impairment [82] and women with RVVC display a decrease in delayed-hypersensitivity to *C. albicans* antigens but react normally to other antigens [83].

There is a strong association between atopy and RVVC [84], and a few studies have shown an association between RVVC and allergy to *C. albicans* [85], allergic conditions such as rhinitis, asthma and other familial allergies [84,86,87]. Higher levels of vaginal anti-candida IgA and IgG have been reported in women with RVVC than those without [86]. *C. albicans* can act as an allergen in some cases and it's been suggested that local hypersensitivity to the yeast can contribute to a prolongation and recurrence of genital candidiasis [84]. In support thereof a few studies have shown benefits from desensitization using *Candida* antigens [87], and clinical response has been observed in about 30% of women with RVVC treated with leukotriene receptor antagonist Zafirlukast [88].

Microbial factors

RVVC is more often due to non-albicans *Candida* such as *C. glabrata* which is less susceptible to the azole antifungal agents [89]. Chong et al. [90] in their study in Malaysia showed that *C. albicans* that cause RVVC are less similar to each other than the strains causing sporadic VVC, thus suggesting that the former may represent more virulent sub-types [90]. Soll et al. [91] reported that although the genotype remains the same there is phenotype switching of *C. albicans* in RVVC [91] and Schroppel et al. [92] observed yeast genetic instability with repeated courses of antifungal treatments [92]. The genetic polymorphic nature of the organisms is considered a major factor in its virulence [93]. The fungistatic mode of action of the azole compounds used to treat VVC and RVVC contributes to fungal recalcitrance to clearance [94], hence the vaginal relapses. There have been concerns that the repeated treatment might induce drug resistance, as well as shift the spectrum of the causative *Candida spp* increasing the chances of non-albicans spp [95,96,97]. Azole resistance has been considered a possible factor in RVVC. Merchaim et al. [98] reported 25 cases of fluconazole resistant *C. albicans* [98]. However other studies have not shown significant drug resistance [15], and therefore it is not considered an issue in RVVC [14,99].

Others

Woman's age (<45 years) and history of VVC have been shown to be strong determinants of a subsequent episode i.e. RVVC [31,52]. Vermitsky et al. [100] reported an increase in percentages of non-albicans *Candida* with increasing age of the woman [100]. Women with RVVC have been shown to be unable to tolerate even small number of Candida compared to healthy women [101]. Mixed infections with BV and VVC are not uncommon and a significant number of women with BV also have yeast residing in the vaginal ecosystem, which can either lead to failure of symptom resolution from therapy targeted at one infection or development of VVC from exposure to antibiotics. Among women diagnosed with bacterial vaginosis (BV), 33.1% were colonized with yeast. This high prevalence of infection/colonization likely predisposes these women to symptomatic VVC after treatment for BV, leading to repeat visits to healthcare providers and higher healthcare costs in general [102].

Diagnosis

Recurrent vulvovaginal candidiasis (RVVC) is often misdiagnosed or over diagnosed, as the diagnosis is based on clinical features – symptoms and signs, which are neither specific nor sensitive. The related symptoms include itching, soreness, vaginal discharge, vulvar swelling, superficial dyspareunia and external dysuria [3,13,103,104]. Of these, pruritus and discharge are the most common complaints [15], and vulvar pruritus and soreness are the only symptoms predictive of a positive yeast culture [14]. The vaginal discharge varies in amount and consistency from watery to homogenously thick – what is referred to as "cottage-cheese like or curd-like and does not have an offensive smell [19,79]. Symptoms may sometimes be aggravated by sexual intercourse, e.g. pruritus [105-107]. The clinical signs include vulvar erythema, fissuring, vulvar swelling (oedema), excoriation, satellite lesions and whitish discharge. The cervix uteri often looks normal [3,13,96,104].

More than 50% of women with symptoms and signs suggestive of genital candidiasis self-reporting may have other conditions [16,108] and since none of the clinical features is pathognomonic for genital candidiasis, corroborative laboratory evidence in necessary. These include:

a) pH test of the vaginal fluid/discharge from the vaginal walls. This should be 4.0-4.5. If it is >4.7 other infections should be considered [3,109], such as bacterial vaginosis, trichomoniasis or mixed infections. This simple test can promptly exclude VVC or two of the most common causes of vaginitis.

b) Microscopy: A wet mount or saline preparation can be done routinely to not only identify yeast cells and mycelia, but also exclude other conditions such as bacterial vaginosis (clue cells) and trichomoniasis (trichomonads). Gram stain of vaginal discharge suspended in or mixed with 10% KOH is said to be more sensitive in identifying yeast cells or hyphae with a 65-85% sensitivity [3,109].

c) Culture: Recovery of yeast in fungal cultures using Sabourad's Dextrose Agar (SDA) remains the gold standard for diagnosing genital candidiasis [3,19,103,104]. Other media used include Nickerson's or Microstix Candida, which are considered similar in performance to SDA [3, 96]. Culture is useful and indicated in patients who either:

A. Have symptom and signs suggestive of genital candidiasis, have a normal pH (4.0 - 4.5), but have a negative microscopy. This is critical as ≥ 50% of patients with culture positive symptomatic genital candidiasis have negative microscopy.

B. Have positive microscopy but fail to respond to the standard therapy i.e. with azole antifungals [94,110,111].

These media do not discriminate among the *Candida spp*. Thus because of the relatively high possibility of non-albicans *Candida* in RVVC, it is at times necessary to use tests which distinguish them. Chromogenic Agar is considered a convenient and reliable means to detect *Candida* and differentiate between *C. albicans* and non-albicans spp. [104]. It has been suggested that it could be used in place of SDA for its advantages which include high yeast recovery rates, differentiation of different *Candida spp*. and identification of polyfungal populations even though it is more costly [98,104].

F) **Other tests:** Susceptibility tests are considered most helpful in patients previously treated with an azole when there is a possibility of antifungal resistance. These are however not considered routine procedures and are not easily available. Furthermore identification of the species is highly predictive of likely susceptibility and can be used as a guide for therapy [8].

Rapid PCR-based assays have been used to detect *C. species* causing RVVC [112,113]. They are said to have high sensitivity and specificity and a shorter turn-around time in comparison to current microscopy and culture techniques. However they are not easily available as a diagnostic test and not considered clinically useful [114]. Pap smear, though specific is insensitive. It is only positive in 25% of patients with culture-positive symptomatic genital candidiasis [3]. Antigen detection and serologic tests are not reliable and not clinically useful [3].

Treatment

The aim of treating patients with RVVC include:-

I. Elimination of potentially reversible risk factors or controlling those not reversible

II. Symptomatic relief as promptly as possible

III. Clearance of the yeast from the genitalia

IV. Prevention of repeat episodes

Once and if potential risk factors are identified, the patient and her sexual partner or spouse should be counselled appropriately and in an empathetic manner, supported to eliminate or control them. Some of the general measures include avoiding tight-fitting synthetic clothing and local irritants e.g. perfumed products [52].The vaginal environment can be altered by changing the contraception to depot-medroxyprogesterone acetate [50].

There are various treatment options for RVVC. The challenge has been to get a drug that can be administered safely, is acceptable, and well tolerated by the patients, thus improving compliance. Treatment of RVVC requires well-tolerated antifungal agents and better understanding of its pathogenesis as well as natural history. There is currently no gold standard for the treatment of RVVC [8]. The principle of therapy involves an induction regimen to ensure clinical remission, followed immediately by a maintenance regimen [3,115,116].

A) Induction therapy

i. Fluconazole – 150 mg orally in three doses given every 72 hours[115,117], or

ii. Clotrimazole 100 mg vaginally daily for 7 days [3,8,115]

1. For azole resistant *Candida spp*,

B) Flucytosine 17% cream either alone or in combination with Amphotericin B 3% cream daily for 14 days, or

C) Boric acid gelatin capsule – 600mg vaginally daily for 14 days [13,94].

D) Maintenance therapy:

i. Fluconazole 150mg orally weekly for 6 months [115], or

ii. Clotrimazole cream 200mg twice weekly or 500mg weekly for 6 months, or

iii. Itraconazole 400mg monthly or 100 weekly for 6 months [3,8,111].

iv. For non-albicans or azole resistant *Candida albicans spp*

v. Boric acid 600mg vaginally once or twice weekly for 6 months, or

vi. Flucytosine 17% cream vaginally either alone or in combination with 3% Amphotericin cream daily for 6 months [3,13,111], or

vii. Gentian Violet 1% weekly for 4-6 months in combination with topical nystatin or Boric acid [13].

viii. In case of recurrence after maintenance regimen each subsequent episode should be treated independently as an acute or sporadic VVC. If recurrence is established induction and maintenance regimens should be instituted.

ix. For pregnant women, avoid oral treatment and use topical azoles and for longer courses [118].

E) Alternative treatment:

a) Use of probiotics – There are anecdotal reports of benefits. Their mode of action is thought to be modulation of the inflammatory process rather than competitive effect with the yeast [119]. In a recent study Vicariotto et al. [120] reported that probiotics reduce recurrences [120].

b) Zafirlukast 20 mg twice daily for 6 months [88] may be considered for those with atopy [84].

c) Cetirizine 10 mg orally daily for 6 months [84].

d) Immunotherapeutic approaches that have been proposed as adjuvant therapy in Candida infections [121].

Discussion

Abnormal vaginal discharge and vulvar pruritus are two very common complaints for which women present to health facilities all over the globe, and genital candidiasis is among the

most common causes thereof. It is considered the second most common cause after bacterial vaginosis accounting for up to 40% in primary health care settings [15]. It is prevalent during the individuals' highest sexual activity and reproductive years i.e. 15 to 40 years. While for the majority it occurs in sporadic form i.e. acute VVC, in a minority (< 10% of those who suffer one episode) it is recurrent, i.e. they experience at least 4 symptomatic episodes in a year [3,79,122].

Whereas it is said to be very common the actual magnitude of VVC and RVVC is unknown. Rathod et al. [123] expressed doubts on the often quoted figures in various publications, and contended that these are higher than the true magnitude of the problem [123]. Recent reports though indicate that the incidence of genital candidiasis is increasing [124]. Cognisant of global increases in some of the key risk factors thereof, such as diabetes mellitus, antibiotic use, and changing individual life-styles and more liberal sexual behaviours and practices which may increase the risk thereto, this assertion may not be far-fetched. This is of particular concern for women in the developing countries such as those in SSA as their life-styles, among other factors are changing rapidly in tandem with globalization and expansion of access to the electronic and/or digital media. Indeed I see more patients with abnormal vaginal discharge now in both private clinic and public health institution than I did some 20 years ago!

The pathogenesis of RVVC remains controversial. Candida, the causative organism, which is part of the normal microbial flora of the lower genital tract in about 20-25% of healthy asymptomatic adult females, is the same organism responsible for symptomatic infection [31,75,102]. The unanswered question is how an organism that is a commensal transforms itself into a pathogen capable of causing such severe and recurring symptoms in the same site. The pathogenesis of RVVC is considered multifactorial with a number of factors acting synergistically to facilitate and enhance *Candida* overgrowth, leading to clinical symptoms. The primary pathology in genital candidiasis is inflammation of the lower genital tract – vulva and vagina, secondary to an overgrowth or abnormal growth of *Candida*. This is thought to be caused more by host factors rather than a more virulent strain or re-introduction of the organism into the genital tract [2], and available evidence suggest an immunological basis for the pathogenesis of genital candidiasis [2,3,125].

Hypothesized risk factors for VVC include pregnancy; a history of VVC; sexual practices, (in particular receptive oral sex); oral contraceptive or replacement therapy; diabetes mellitus and immunodeficiency states [6,72,78,126]. However, definitive evidence relating to each of these factors is limited [7,78]. Epidemiologic studies have failed to measure the true attack rate and have been unable to specifically identify characteristics of the at-risk subpopulation [7,57]. The variation may be due to diagnostic criteria, methodological or study population differences.

Of special interest and concern for the SSA and in particular the Eastern, Central and Southern Africa sub-regions, is the reported association between genital candidiasis and HIV/AIDS, because of the comparatively high prevalence of the latter [37,39]. HIV infection is involved in changes in the normal vaginal flora that favour the development of local infections, which in turn lead to increased local viral replication [127,128]. These increase sexual transmission of HIV [129]. Genital candidiasis is more frequently diagnosed and with greater persistence in HIV infected women than uninfected [36]. HIV/AIDS have been cited as major contributing factors to the increase in the incidence of fungal infections [130,131]. There is also higher diversity of non-albicans *Candida spp* in HIV infected women [38]. Spinillo et al. [132] reported that these patients have higher frequency of *C. glabrata* and are more prone to recurrence than HIV-negative controls [132]. There is also higher diversity of non-albicans *Candida spp* [38]. The extensive use of prophylactic antifungal for opportunistic infections in HIV/AIDS may increase non-albicans spp in RVVC as well as resistance of *C. albicans* to the common azole compounds used [36,40], thus complicating treatment thereof. There are also concerns that RVVC may increase the risk of HIV acquisition [133]. Rottigen et al. [134] reported a two-fold increase in the risk of HIV acquisition in women with genital candidiasis compared to the uninfected [134]. Apalata et al. [39] reported that genital candidiasis was associated with genital shedding of HIV (p=0.0002) [39]. This was supported by Wang et al. [135]. Simon et al. [136] opined that genital candidiasis may contribute to an increase in population level risk of HIV infection [136]. There are also concerns that use of topical azole for treatment of genital candidiasis may affect the integrity of the latex condom, thus increasing risk of HIV transmission! All these present serious challenges with treatment of RVVC as well as HIV/AIDS in countries with high incidence thereof, such as the developing countries of SSA. Could the foregoing therefore account at least in part for the fact that women in SSA are more susceptible to HIV infection and could it also explain the relatively higher prevalence of HIV/AIDS in young sexually active women? If that is true, there is an urgent need to include in the preventive strategies screening and treatment of genital candidiasis! Indeed Goel et al. [137] in their study in India noted that the prevalence of reproductive tract infections (RTI) including candidiasis in HIV-seropositive women was high enough to warrant routine gynaecological evaluation and RTI screening in these patients [137]. Occurrence and recurrence of opportunistic infections in HIV positive individuals is a challenge faced by clinicians worldwide. Although the majority of cases of recurrent vulvovaginal candidiasis (VVC) develop without predisposing factors, it is a common problem in women with HIV infection. Considering all the above and as one of the studies has effectively demonstrated that non albicans strains (which are more resistant) do develop as a result of VVC prophylaxis with fluconazole; the question therefore is whether routine prophylaxis should be given at all to HIV positive women for VVC on the basis of the present evidence or whether more trials are required which include and investigate all the above aspects before a judgment can be made as regards routine prophylaxis of VVC in HIV positive. Azoles are the mainstay of the treatment of candidiasis in any form and development of resistance to these drugs would not be desirable especially since VVC rarely if ever leads to systemic candidiasis or other such life threatening situation which makes waiting until the VVC appears before starting treatment an alternative to prophylaxis.

The theory that recurrence may be due to reinfection of the woman by her male sexual partner has been suggested repeatedly with some data indicating that sexual transmission does occur [65,66,69]. *Candida spp* may be harboured in the male GIT, semen, oral cavity and urine [78,138], and male colonization is often associated with vaginal colonization often with the same strain of Candida [66,139]. Studies have indicated that oral sex performed by the male partner (cunnilingus) is associated with both incident and recurrent candidiasis [65,69]. Bailey et al. [67] reported an increased risk of genital candidiasis among women who have sex with women (WSW), which rose with number of partners [67]. Although they concluded that this possible sexual transmission whatever WSW practice, often include oral sex, as well as other sexual practices/activities. They however did not report on the actual practice these women did with each other! Indeed Reed [78] had suggested that it is the sexual behaviours rather the presence of *Candida spp* at various body locations of the male partners that are associated with recurrences of genital candidiasis [78]. Receptive oral sex has become fashionable and part of many young partners' sexual repertoire even in the developing world in lieu of penetrative sexual intercourse or part of the foreplay. This has the potential of increasing prevalence of VVC and RVVC in young sexually active women! The role of sexual transmission has yet to be defined. Clarification of this controversy could avoid unnecessary treatment of sexual partners, thus reducing costs, side effects and conflict among couples.

Although the widespread use of antibiotics has been suggested as one of the major factors contributing to the rising incidence of genital candidiasis [45,126], the supportive evidence has been limited. [57]. Accordingly, existing data on the risk of developing antibiotic-associated VVC are conflicting [57,78,126]; For example, some case-control studies [6] found no evidence of an association between antibiotic agents and symptomatic VCC, whereas others reached the opposite conclusion. Results from a prospective study of 250 pregnant women concluded that extensive antibiotic use posed little risk for the development of yeast infection [51]. Antibiotic use is known to increase colonisation with yeast. The precise relationship between yeast colonization and symptomatic yeast vaginitis is not entirely clear. However yeast colonization is considered a necessary precursor for subsequent symptomatic VVC [7]. Bluestein et al. [56] reported a 35% *Candida* colonization at baseline that increased to 50% after 10 days of antibiotic therapy [56]. Pirotta et al. [140] reported increased *Candida* colonization from 21% at baseline to 37% 2 weeks after antibiotics use and 23% of women developed symptomatic VVC after antibiotics [140]. Critical factors determining individual susceptibility to antibiotic-associated VVC remain to be determined.

Diagnosis of genital candidiasis including RVVC is usually made on the basis of clinical signs and symptoms [140] without even the benefit of physical examination and/or laboratory tests in most of our clinical settings. Some patients even self-medicate with over-the-counter prescriptions. Some of the reasons for this include financial constraints, lack of diagnostic facilities and awareness of the value of confirmatory laboratory tests. However even when they are performed, they are not conclusive and do not necessarily confirm the diagnosis. This may be due to the fact that about 20-25% of healthy women are colonized in their vagina by Candida, the clinical features are not pathognomonic of genital candidiasis and the presence of non-albicans spp such as *C. glabrata* which is not easily recognized on microscopy as it does not form hyphae or pseudohyphae. In a large study involving women attending an STD clinic, Eckert et al. [109] found that only 28% of women with symptoms suggestive of candidiasis (n=545) were Candida culture positive [109]. This is indeed a big challenge and of major concerns for the developing countries, as laboratory diagnosis is considered essential in RVVC [100], but is not always available and when it is done and treatment based on the results thereto, one can't be sure that the patient in question actually had genital candidiasis and not other conditions!

There is currently no gold standard treatment of RVVC. The recommended regimens including induction therapy at times up to two weeks followed by maintenance therapy for up to six months, which have been supported by randomized clinical trials [115], have numerous challenges. The repeated treatments may increase the likelihood of drug resistance as well as shift the spectrum of causative *Candida spp* [76,89,95- 97]. The same has been said with regards to widespread use of azole compounds especially when the diagnosis is not confirmed [14,142]. MacNeill et al. [143] suggested that the increase in the number of women with RVVC can be attributable to over-the-counter antifungal prescriptions [143]. The high prevalence of non-albicans *Candida spp* in RVVC which has been shown to be more common in the developing countries is a worrying situation as *C. glabrata* has been shown to have high minimum inhibitory concentration (MIC) to azole, and *C. krusei* is intrinsically resistant to fluconazole [131,144]. Richter et al. [89] reported that 67% of *C. glabrata* from vaginal isolates were not susceptible to azole compounds [89]. Though boric acid is very effective in their treatment its efficacy ends with cessation of treatment [89]. The long duration of treatment ≥ 6 months has the potential of impacting on compliance, which may worsen recurrences. It may also lead to colonisation with less susceptible *Candida spp* or development of resistance among usually susceptible *Candida albicans* strains and ultimately to refractory candidiasis [11,145]. The fact that there is no cure even after such a prolonged treatment course, with 60-70% having a recurrent episode within two months [94,116], may lead to frustration among the patients who may not accept and/or use antifungals for the next episode. Martinez [146] reported that the frequent and/or long-term antifungal therapy may predispose to bacterial vaginosis [146], and Patel et al. [52] observed that young women with bacterial vaginosis may have an increased risk of genital candidiasis [52].

There have been efforts to identify preventive strategies for RVVC, which have not been very successful basically because on non-resolution of the pathogenesis, the risk factors and protective factors. Contrary to the commonly posited hypothesis that vaginal lactobacillus colonisation has a protective effect, McClelland [102] found that such colonization was in fact associated with nearly four-fold increase in the likelihood of symptomatic genital candidiasis [102]. Pirotta et al. [140] reported that neither oral nor vaginal lactobacillus administration prevented genital candidiasis following antibiotic use [54]. Falagas et al. [147] reviewed publications on use probiotics for prevention of RVVC, and noted that the available evidence for the use of probiotics for

prevention of recurrent VVC is limited. Most of the relevant clinical trials had methodological problems such as small sample sizes, no control groups (placebo) and included women without confirmed recurrent VVC. They contended though that empirical use of probiotics may be considered in women with RVVC, especially for those who have adverse effects from or contraindications for the use of antifungal agents, since adverse effects of probiotics are very rare [147]. In a more recent study Vicariotto et al. [120] reported that probiotics reduce recurrences [120]. However their sample size was also very small.

A few studies have shown some benefits from desensitization programmes using Candida antigens [54,87]. It is not clear how big the magnitude of benefit and who is best suited for that. New insights into the mechanisms of the anti-Candida host response have contributed to the design of novel immunotherapeutic approaches that have been proposed as adjuvant therapy in *Candida* infections [121]. Immunotherapy is considered a potential new frontier in the management of candidiasis. The need to personalize treatment of RVVC has been advocated for [148], which has been shown to improve compliance and efficacy thereof.

Conclusions and Recommendations

RVVC remains an intractable problem for clinicians and patients alike inspite of major therapeutic advances globally. RVVC is a highly troublesome and emotionally traumatic condition for women. It is a source of considerable physical discomfort. It affects the woman's quality of life and may impact negatively on her sexual life as well. The latter may be due to the associated dyspareunia, fear of triggering a crisis or infecting ones partner. Some may avoid sexual intimacy with their partners as the symptomatic episodes may be associated with recent and/or frequency of sexual intercourse or particular sexual practice. The woman's social and professional lives may also be seriously affected by the recurring symptoms for which there is no cure. Others may feel embarrassed and therefore psychologically affected because genital candidiasis is still regarded as a sexually transmitted infection, by both health providers and the general public despite evidence to the contrary! The associated costs of medical visits are high.

All health care providers need to be aware of the pathogenesis, potential risk factors, the value of confirmatory laboratory tests and which ones, as well as appropriate management for RVVC. They should also take cognizance of the challenges thereto. Of critical importance especially for primary care health workers are women who may present with dysuria as some of these may be due to genital candidiasis and routine antibiotic prescription as is often the practice may only serve to worsen the symptoms. Cognisant of the magnitude of the problem and associated effects such as cost, impact on the woman's life and the potential of increase as outlined above, there is need for locally relevant research studies to better understand genital candidiasis in the local context. They may include predisposing factors, preventive strategies, drugs and drug regimens for RVVC treatment especially in HIV infected women. There is also need for national or regional guidelines for its management.

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