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Vulvovaginal candidiasis in married women between age 25 to 45 years old

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Dedication

I dedicate this work to the ***Almighty God***, thank you for the guidance, strength, power of mind, protection and skills and for giving me a chance to be a good doctor.

It is a great pleasure to dedicate this work with my thanks and respect to my supervisor ***Prof Dr. Luma T. Ahmed*** for her valuable instructions.

To all my family member, who shared their words of advice and encouragement to finish this study.

Abstract

Background: vulvovaginal candidiasis is a common infection among reproductive age group females. There was a significant association between VVC and sexual activity, pregnancy, contraceptive use, hormone replacement therapy and others like DM, HIV. VVC is mostly caused by overgrowth of candida species in the vagina and is characterized by curd like vaginal discharge, itching and erythema.

Objective: the purpose of this article review is:

1. To know why VVC is more common in women between the ages of 25-45 years old?!
2. To know the distribution of VVC in this age group (25-45 years old) in both pregnant and non- pregnant women?!
3. To know the causes of VVC in order of frequency (both medical and non-medical ones)?!

Method: I searched for these articles on google scholer, pumbed, research gate.

Conclusion: I concluded that VVC is more common in women of reproductive age group, therefore routine high vaginal swab should be performed in these women even asymptomatic. In one of these studies, VVC prevalence was found to be 31.69%, while its prevalence in nulliparous women 25.4% and in women with more than 2 child is 40% which is higher than nulliparous one. Previous candidiasis was the most common risk factor associated with VVC (66%) followed by DM (56%), IUCD(40%), OC pill(28%), and pregnancy(26%). Imidazole is the drug of choice, and in RVVC a more prolonged courses may be needed.

Keywords: vulvovaginal candidiasis (VVC), recurrent vulvovaginal candidiasis (RVVC), high vaginal swab(HVS), intrauterine contraceptive device(IUCD), oral contraceptive pills (OC pills).

Introduction

Vulvovaginal candidiasis is a frequent distressing disease affecting women of all ages. It is mostly caused by *Candida albicans* (90% of cases) which are part of the lower genital tract flora in 20-50% of healthy asymptomaic women (McClelland RS *et al*,. 2009). It is not a sexually transmitted disease and is the second most common cause of vaginal infection (barouse MM *et* al., 2005). Approximately 75% of women of childbearing age will have at least one attack of VVC and 5% of these women will have a recurrent vulvovaginal candidiasis (Fidel *et al.,* 2015). The rates are highest in women of reproductive age 20-45 years old, pregnant women, postmenopausal women on hormonal replacement therapy (sobel J *et al*,. 2012). It is rare in pre-pubertal and post-menopausal women, it is thought to be due to higher estrogen levels in these women that increase glycogen content in the vagina and thus affect positively on candida growth and increases its adherence to the vaginal

epithelium (Mardh P *et al*., 2014). The primary pathology is inflammation of vulva and vagina due to candida overgrowth (Edwards L *et al*., 2011). The symptoms and signs are not specific. It is classified as complicated or uncomplicated VVC (Pappas JD *et al*,. 2009) or as a sporadic (acute) and recurrent depending on frequency of infectious episodes (El-Din SS *et al.* ,2011).

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)

Table(1) : classification of vulvovaginal candidiasis (M Lema V *et al*,.2017).

Some patient may remain asymptomatic, while others may experience intense vulvar and vaginal itching, thick white discharge, and dysuria. VVC diagnosis is confirmed by microscopic examination of vaginal swab with 10% solution of KOH, it dissolves the skin cells allowing a better visualization. Imidazole is the drug of choice for VVC, it can be applied topically or be administered orally. Seven, six, and three days dosing therapy can be used (Marie Berry *et al*,. 2016).

Recurrent vulvuvaginal candidiasis is defined as 4 or more episodes of VVC or at least 3 episodes not related to antibiotic therapy (Sheary B *et al*,. 2015). It is requires identification and treatment or avoidance of its risk factors and a longer courses of treatment (Ringdahl EN *et al*,. 2016).

Distribution of vulvovaginal candidiasis according to age

In North West Nigeria the prevalence is high due to low socioeconomic status, improper hygiene, less education, and African ethnicity (Ugwa EA et al,.2015). In some studies the highest number of VVC was in 26-30 years age group(39.08%) followed by 31-35 years age group (30.18%) which is similar to study done by EA Ugwa and Yadav K et al (Ugwa EA et al,.2015), (Yadav K et al,.2016). Yadav K et al, found the highest number of VVC were in 21-25 years age group (40.44%) followed by 26-30 years age group (32.58%). Women above 45 years have the lowest prevalence (14%), as advancement in age will lower estrogen effect in women, and thus lower infection rates, in addition to that they are mostly not sexually active. 19.71% of nulliparous and 80.28% of multiparous women were positive for candida, this may be due to higher sexual activity, poor personal hygiene, and the use of contraceptive devices in multiparous ones (Salvi M et al,.2018).

			Candida		
			Positive	Negative	Total
Age (Years)	20-25	Count % within age group	2 (22.22%)	7 (77.78%)	9 (100%)
	26-30	Count % within age group	34 (39.08%)	53 (60.92%)	87 (100%)
	31-35	Count % within age group	16 (30.18%)	37 (69.82%)	53 (100%)
	36-40	Count % within age group	16 (29.62%)	38 (70.38%)	54 (100%)
	>40	Count % within age Group	3 (14.28%)	18 (85.72%)	21 (100%)

Table (2): VVC distribution according to age (Salvi M *et al*,.2018)**.**

Pathogenesis

1. Vulvovaginal candidiasis as an immunopathology :

For decades, VVC was regarded by many studies is the disease that may result from defective adaptive immune response, but another several cross-sectional clinical studies revealed that HIV women (with reduced

CD4 and T cell count) are not greater risk factor for VVC development as compared to healthy women (Mendling *et al*,. 2011). A study using volunteer from women, which are intra-vaginally challenged with live *C.albicans* revealed that VVC was mediated by host innate immune response with neutrophil requirement into vaginal lumen was positively correlated with disease symptoms (Peter *et al*,. 2012). Due to negative impact of host immunity on disease progression, VVC was considered as immunopathology (Black, C.A *et al*,. 2012).

These study results raised 2 questions:

- Do neutrophils help clear the fungus?
- Are neutrophils themselves causative agents of damage?

Depletion of neutrophils by neutralizing antibody do not reduce fungal load or vaginal LDH levels during infection, suggested that neutrophils are not protective in such conditions and mucosal damage is mediated by fungus (Peter *et al*,. 2012). In another study, neutrophil depletion indeed reduced vaginal inflammation, but ultimately did not impact colonization and course of infection (Black, C.A *et al*,. 2012).

2. Sensing fungi at the vaginal mucosa :

C. albicans must first be sensed at the mucosal interface prior to initiation of an immune response. It is mediated by pattern recognition receptors at the cellular surface of epithelial an innate immune cells. Activation of these receptors by candida cell wall constituents induce pro-inflammatory cytokine signaling and the recruitment of both innate and adaptive immune cells to infectious foci (Cheng S.C *et al*,. 2012).

3. Invasion and secreted virulence factors:

Candida exerts their damage through 2 major mechanisms:

- Direct hyphal filaments invasion: hyphae are very important in causing mucosal invasion and tissue damage by degratative enzymes secreted at hyphal tip and the pressure exerted by the elongated filaments (Lew, R.R. *et al,*. 2011). Mucosal invasion begins within 3 hours and continual hyphal growth is required for damage (Wachtler, B. *et al,*. 2011). Hyphae associated adhesions help anchor candida to mucosal epithelium and in vivo, are important for mature biofilm formation (Harriott *et al,*. 2010).
- Secreted factors: the aspartyl proteinase and lipase gene families are the most studied. SAPs degrade the extracellular proteins to be used as metabolic nitrogen sources (Schaler *et al,*. 2011). SAPS 1-3 are largely associated with expression in the yeast cell and at PH 2-5, while SAPS 4-6 are expressed during hyphal growth with PH 5-7 (De Bernardis *et al,*. 2011). Lipases have an essential role in the hydrolysis and synthesis of triglycerols (Schofield *et al,*. 2015).

3. Others: such as candidalysin, IL-17, NLRP3, and estrogen dependent immunomodulation (Gacser *et al,*. 2007).

Risk factors

1. Previous candidiasis

   This was reported as the most important risk factor(66% of VVC have a previous history of the same condition) (Salvi M *et al,*. 2018).

2. Diabetes mellitus

Vaginal colonization with candida is more common in diabetes than non-diabetic women, and those with DM2 more susceptible to vaginal

colonization with non *Candida albicans* especially *C. glabrata* (De Leon EM *et al*,. 2012).

3. Immunosuppression

   HIV is a risk factor for symptomatic candida infection (Ray A *et al*,. 2011). Some studies have shown that increased incidence of colonization with candida and symptomatic candidiasis are associated with decreased CD4 cell count especially below 200 cells/mm^3 (Duerr A *et al*,. 2013). HIV patient have shown increased incidence of non-*Candida albicans* colonization more than HIV negative women (Aplata T *et al*,. 2014).

   Corticosteroids use have been reported to increase the incidence of symptomatic candida infection (Ohmit SE *et al*,. 2013).

4. Contraception

   Its role as a risk factor remains controversial. Whereas low estrogen contraceptives have been shown to increase genital candidiasis (Cetin M *et al*,. 2007), similar things is noted with high estrogen contraceptives (Barbone F *et al*,. 2013).

   Women using IUCD, contraceptive sponges, diaphragm, and condoms with or without spermicides, have reported an increased rates of vaginal colonization with candida (Demirezen S *et al*,. 2015).

5. Pregnancy

   In pregnancy, the high concentration of reproductive hormones especially estrogen, increases the glycogen content in the vaginal epithelial cells which increases the risk of symptomatic candidiasis (Dennerstein S *et al*,.2011).

6. Antibiotic therapy

Antibiotic eliminate the protective bacterial flora in the vagina (lactobacillus), thus permitting yeast overgrowth (Pultz NJ *et al,*. 2015). It has been reported that 28-33% of women using antibiotic therapy develop symptomatic genital candidiasis (Pirotta MV *et al,*. 2013).

It is worth to noting that the great majority of women with genital candidiasis have not used antibiotic (Glover DD *et al,*. 2013). In another studies, did not show an association between VVC and antibiotic use, and patients who develop genital candidiasis following antibiotic use are already colonized in their vagina with candid, while this may be true but it does not explain how antibiotic transform the candida from commensals to a pathogen (Pirotta MV *et al,*. 2013).

7. Behavioral factors

   Genital hygiene habits such as douching, use of sprays, deodorants, and medicated soaps on/in genitalia increase the risk of VVC/RVVC (Ekpenyong CE *et al,*. 2012), in addition to wear of tight clothes, non-cotton under-wears, which increase local humidity and temperature, thus increase the risk of VVC (Patel DA *et al,*. 2014).

8. Dietary factors

   Some studies, suggest that diet rich in sugar content may increase the risk of genital candidiasis (Akah PA *et al,*. 2010), but other studies did not find an evidence to support the role of sugar (Reed BD *et al,*. 2011).

Clinical presentation

The clinical symptoms of VVC are non-specific and can be associated with wide variety of vaginal diseases such as trichomoniasis, bacterial

vaginosis, gonorrhea /chlamydia infection. The hallmark symptoms are pruritus and burning sensation that is accompanied with thick curdy vaginal discharge, there may be soreness, irritation, dysuria or even dyspareunia.

On examination, vulvar and vaginal erythema, edema, fissures, discharge may be found.

Patient with infection by *candida glabrata* usually have less severe symptoms (Jeanmonod R *et al* ,. 2020).

Differential diagnosis

1. Vulval dermatitis-allergic and irritant.
2. Trichomoniasis.
3. Genital herpes.
4. Bacterial vaginosis.
5. Chlamydia and gonorrheal infection.
6. UTI.
7. Vestibulitis (Belinda S *et al*., 2005).

Diagnosis

Laboratory tests that may be used to confirm VVC are:

1. Microscopy: saline preparation or wet amount can be used routinely to identify yeast cells and mycelia, and to exclude other differential diagnosis. Gram stain of vaginal discharge mixed with 10%KOH have a sensitivity of 65-85% (Sobel J *et al*,. 2012).
2. Culture: sabourad's dextrose agar remain the gold standard for diagnosing genital candidiasis. Other media used include nickerson's or microstix candida. These media do not differentiate between candida species, on the other hand chromogenic agar is a

reliable and very useful in differentiating between *candida albicans* and other candida species. Its advantages are high yeast recovery rates and identification of poly-fungal populations even though it is more costly (Sobel J et al,. 2012). Culturing is indicated in patien :

- Have symptoms and sins suggestive of genital candidiasis with normal PH (4-4.5), but have negative microscopy. This is very important as more than a half of symptomatic patient with positive culture have a negative microscopy (Sobel J et al,. 2012).
- Have positive microscopy but fail to improve with standard therapy (Sobel J et al,. 2012).

Treatment

VVC is treated with antifungal agents. Since the vast majority of cases are secondary to *C. albicans* and since it does not have significant resistance to azoles, these are the treatment of choice. It may be taken orally as a single dose (fluconazole 150) or be applied intra-vaginally in a single day or three day regimens (Jeanmonod R et al,. 2020).

- In non-complicated cases (those without immunosuppression/pregnancy), either therapy is effective, so decision is made upon patient preference, cost, and drug interactions. If there is no response to standard therapy, culturing is advised to detect the resistant strains of candida (Jeanmonod R et al,. 2020).
- In complicated cases, patients often require longer therapy typically involves intra-vaginal azoles for at least one week duration, or oral fluconazole 150mg (renal adjustment if creatinine

clearance < 50ml/min) 3 doses, once every 3 days (Jeanmonod R et al,. 2020).

- In pregnant women, intra-vaginal fluconazole for 7 days may be appropriate. Oral fluconazole is contraindicated in pregnancy, but is considered safe in breastfeeding (Jeanmonod R et al,. 2020).
- There is in adequate evidence to support intra-vaginal garlic, or douching, or even oral yogurt therapy (Jeanmonod R et al,. 2020).

Table 2. Treatments for vulvovaginal candidiasis

Polyenes
- nystatin, topical

Azoles
- imidazoles
  - clotriamazole, topical
  - miconazole, topical
  - ketoconazole*, oral
- triazoles
  - fluconazole**, oral

Other
- boric acid intravaginal capsules
- flucytosine, topical

Table(3): treatment of vulvovaginal candidiasis (Jeanmonod R *et al*,. 2020).

Non *candida albicans* vulvovaginal candidiasis

Non *candida albicans* species may be resistant to conventional treatment with azole therapy. Species identification and azole sensitivity can be requested on culture. *C. glabrata* is the most commonly found non candida albican species, others include *C. tropicalis, C. krusei*. As *C. glabrata* has a poor in vitro response to fluconazole, thus it is not recommended to use it as the first line of treatment (Belinda S *et al*,. 2005).

Recurrent vulvovaginal candidiasis

Recurrent vulvovaginal candidiasis is defined as 3-4 attacks of VVC with white " cottage cheese " vaginal discharge, itchiness, and other symptoms of VVC in one year duration with at least partial improvement of symptoms between episodes and positive microscopy/ culture on at least 2 occasions when symptomatic. It is classified as primary and secondary RVVC. Primary RVVC is idiopathic and thought to occur in healthy, immunocompetent women, vast majority of them have no known predisposing factors, while secondary RVVC is due to known predisposing factors such as DM, hormonal replacement therapy (Fidel PL *et al*,. 2015).

It is diagnosed and treated mainly clinically, without confirmatory laboratory tests. In RVVC, there is differences in intensity of symptoms between different episodes, which may cause significant physical, psychological and social morbidity, as well as adverse effect on sexual activity (Fidel PL et al,. 2015).

Pathogenesis and risk factors for RVVC

Two theories have been proposed to understand the RVVC:

1. Post-treatment relapse.
2. Post-treatment reinfection.

Post-treatment relapse theory is the preferred one in patient who experienced a sequential episodes of RVVC, which are caused by the same type of candida. In a retrospective review, found 8 of 10 patient with RVVC over a mean of 3 years have demonstrated the same *C.albicans* strain.

In secondary VVC, either microbial factors chiefly consists of non-*albicans candida* species mostly *candida glabrata* /or host factors including systemic corticosteroids, the use of antibacterial, uncontrolled DM, thyroid disease, HIV (which impair immune system of the host) are the responsible factors for RVVC. Resistant candida is not common (Sobel J *et al* ,. 2012).

In a new study, a lot of behavioral factors such as sexual practices, clothing habit, and diet may responsible for RVVC (Fidel PL *et al*,.2015).

Diagnosis

In RVVC, culture/microscopy showing spores or pseudo-hyphae is especially important in confirming the candidiasis. Culture is very important to ensure an appropriate treatment will be given. It seems that in symptomatic period, 2 consecutive negative cultures is adequate to exclude RVVC.

Rapid PCR assays may be used to identify candida species causing RVVC. It is not easily available and not useful clinically (Belinda S *et al* ,. 2005).

Treatment of RVVC

The aim of treating patient with RVVC:

1. Elimination of potentially reversible risk factors or controlling the non-reversible one.
2. Improve symptoms as soon as possible.
3. Clearance of the candida from genital tract.
4. Prevention of recurrence of genital infection.

There are no standard treatment for RVVC treatment. It include an induction regimen followed immediately by a maintenance therapy:

1. Induction therapy :
    - Fluconazole-150mg orally in 3 doses regimen every 72 hours.
    - Clotrimazole-100mg vaginally each day for 7 days.
    - For azole resistant *candida spp*:
        - Flucytosine cream 17% either alone or in combination with amphotericin B cream 3% daily for 14 days or,
        - Boric acid gelatin capsule-600mg vaginally each day for 2 weeks.
2. Maintenance therapy:
    - Fluconazole 150mg orally each week for 6 months or,
    - Clotrimazole cream 200mg twice each week or 500mg each week for 6 months, or
    - Itraconazole 400mg each month or 100 each week for 6 months.
    - For *non-albicans* or antifungal resistant spicies :
        - Boric acid 600mg vaginally once or twice each week for 6 months, or
        - Flucytosine cream 17% vaginally either alone or in combination with amphotericin B 3% daily for 6 months, or
        - Gentian violet 1% each week for 4-6 months in combination with topical nystatin or boric acid.
    - If there is recurrence after maintenance therapy, each episode should be treated as an acute or sporadic VVC.
    - In pregnancy, use of topical antifungal for longer duration is recommended. Oral azoles are contraindicated.
3. Alternative treatment:

- Probiotics: there are evidence supports its use. Their mechanisms of action is to modulate the inflammatory process rather than competitive effect with the candida. Recent studies reported that it reduce recurrence
- Zafirlukast 20mg twice daily for 6 months. It may be useful for patients with atopy
- Cetirizine 10mg orally each day for 6 months
- Immunotherapeutic measures as an adjuvant therapy in candida infection (M Lema V *et al* ,. 2017).

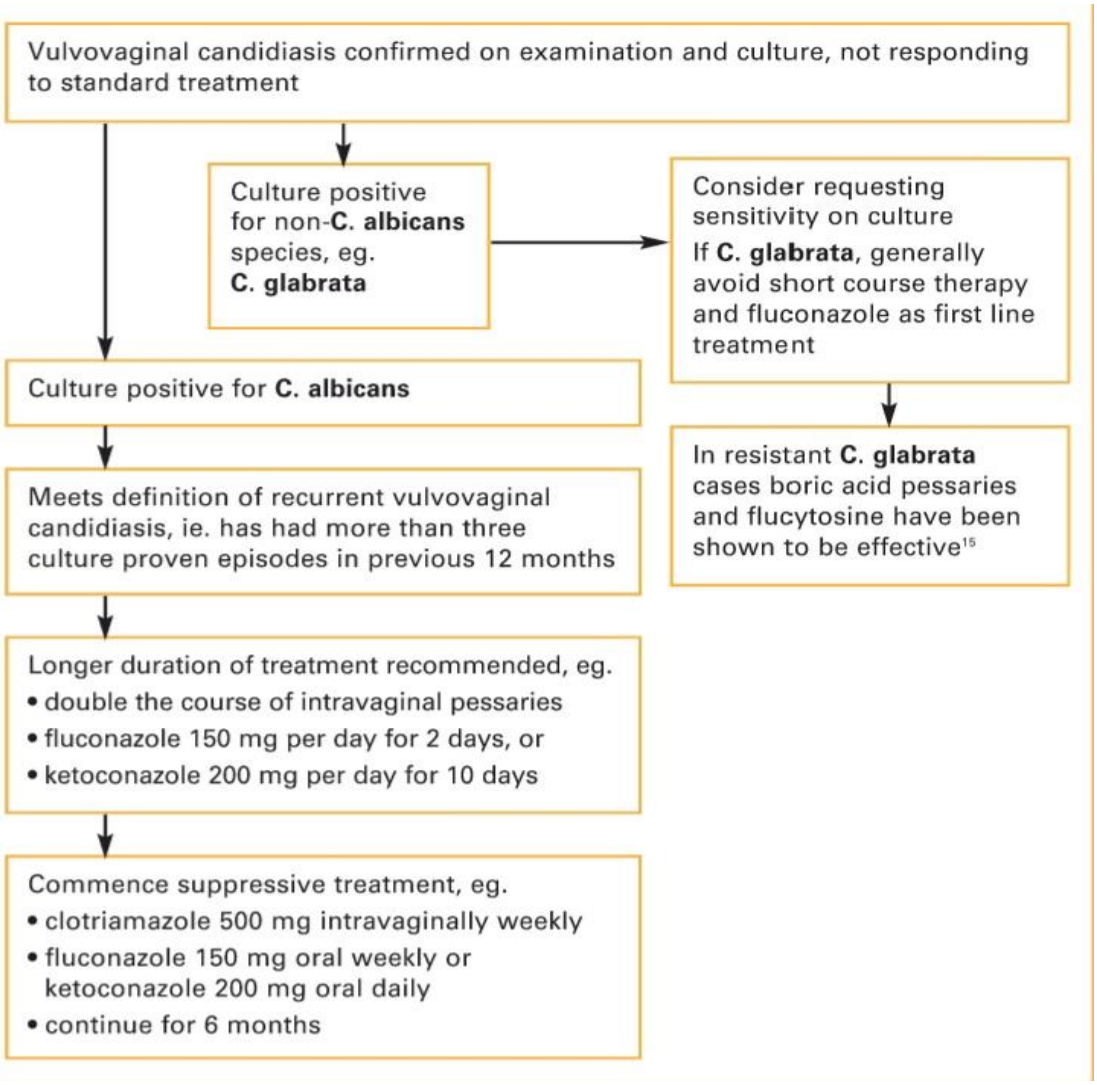

Figure (1): management of VVC not responding to standard treatment (M Lema V et al,. 2017).

Discussion

The exact prevalence of VVC is difficult to estimate, because most cases are diagnosed clinically without confirmatory microscopy or culture (as half of these patient who diagnosed clinically may have another disease). Young women who are sexually active have low vaginal defense mechanisms against candida, in addition to use of oral contraceptive use and other risk factors that may contribute to higher prevalence VVC in this age group. Women above 45 years have the lowest prevalence (14%), as advancement in age will lower estrogen effect in women, and thus lower infection rates, in addition to that they are mostly not sexually active. 19.71% of nulliparous and 80.28% of multiparous women were positive for candida, this may be due to higher sexual activity, poor personal hygiene, and the use of contraceptive devices in multiparous ones. Finally, previous candidiasis was the most important risk factor (66% of VVC cases), followed by DM (56%), IUCD (40%), OCPill (28%), pregnancy (26%) (Salvi M *et al*,.2018).

Conclusion

From this article review I concluded that VVC is more prevalent in reproductive age group women because young women who are sexually active have low vaginal defense mechanisms against candida. In addition there was a strong correlation between the prevalence of VVC in young women and contraceptive use, IUCD use, pregnancy, poor genital hygiene. Therefore a routine HVS in these women is essential even if asymptomatic. All women should be educated about the signs and symptoms of VVC and personal hygiene. Future studies is needed to know the exact prevalence of VVC in both pre-pubertal and postmenopausal ones.

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