SLCOG Sri Lanka Journal of Obstetrics and Gynaecology

Management of Candida Vulvovaginitis

Guideline No: 01

December 2022

Please cite this paper as: De Silva PHP et al, on behalf of Sri Lanka College of Obstetricians and Gynaecologists. Management of Candida Vulvovaginitis.

Sri Lanka College of Obstetricians and Gynaecologists

Management of candida vulvovaginitis

P H P de Silva[a], **S Lanerolle**[b], **H S Dodampahala**[c], **W Galapaththy**[d], **C Mathota**[e], **S A Karunananda**[f] ***on behalf of the Sri Lanka College of Obstetricians and Gynaecologists***

Correspondence: Sri Lanka College of Obstetricians and Gynaecologists, No. 112, Model Farm Road, Colombo 08. E-mail: slcogoffice@gmail.com

Infections in the vulva and vagina are not uncommon. Although most infections are not life threatening, they cause great discomfort and suffering in the affected woman. The symptoms associated with vulvovaginal infection are primarily that of discharge, discomfort, soreness and itching. However, the association between the presence of vulvovaginal infection and symptoms are not clear-cut and straightforward. In this context, it is important to understand the precise state of infection from mere colonization by Candida. Accurate diagnosis is critical to successful treatment.

The most common reasons for vulvovaginitis are

- Vulvovaginal Candidiasis (VVC) – (17% - 39% of cases)
- Bacterial Vaginosis (22% - 50% of cases)
- Trichomoniasis (from 4% - 35% of cases)
- Undiagnosed presence of vaginitis is reported in 72% of cases[1].

However in pregnancy, Candidiasis is the commonest cause of vulvovaginal inflammation and infection. In vulvovaginal inflammatory conditions, infections mentioned above are the commonest. But vulvar skin diseases ranging from atrophic inflammation related to estrogen deprivation, specific and non-specific skin conditions affecting the vulva (eg. vulvar skin diseases, desquamative inflammatory vaginitis etc.) are encountered in clinical practice.

This guideline focuses on Candidiasis as the primary cause for vulvovaginitis.

As per common literature supported by British Association of Sexual Health and HIV National Guidelines – BASHH 2019 Candida infection is divided into two.

1. Acute VVC (An isolated presentation of VVC)
2. Recurrent VVC (At least four episodes in 12 months; but two episodes should be confirmed by microscopy or culture. At least one of these should be a culture diagnosis.

Of the patients with recurrent VVC, two groups could be identified. Those who respond well to therapy and those who do not.

Pathophysiology

Candida is a yeast. They are eukaryotic organisms which are unicellular. They have the ability to develop multicellular characteristics, hence the appearance of pseudohyphae. Candida is a common organism found

Sri Lanka Journal of Obstetrics and Gynaecology 2022; **44:** 249-256

DOI: http://doi.org/10.4038/sljog.v44i4.8077

[a] *Consultant Obstetrician and Gynaecologist, Colombo North Teaching Hospital, Ragama, Sri Lanka.*

[b] *Consultant Obstetrician and Gynaecologist, Castle Street Hospital for Women, Colombo 8, Sri Lanka.*

[c] *Professor in Obstetrics and Gynaecology, Department of Obstetrics and Gynaecology, University of Colombo, Sri Lanka.*

[d] *Consultant Obstetrician and Gynaecologist, Karawanella Base Hospital, Sri Lanka.*

[e] *Consultant Obstetrician and Gynaecologist, Colombo North Teaching Hospital, Ragama, Sri Lanka.*

[f] *Senior Lecturer and Clinical Professor of Obstetrics and Gynaecology, University of Peradeniya, Faculty of Medicine, Sri Lanka.*

in low numbers in human skin moist areas and female genital tract. Out of all cases of candida vulvovaginitis, 80% - 89% of VVC is by *Candida albicans*. The rest are due to other sub-groups mentioned below.

Although antifungal agents are used by various medical practitioners, clinical resistance to azoles is rare in Candida[2,3,4]. No reports of spontaneous emergence of azole resistance in candida has been reported[5,6]. The MIC (Minimum Inhibitory Concentration) of antifungal agents are tested at a pH of 7. In the acidic environment of vagina, azoles are known to reduce their efficiency; the required concentration for control hence would be higher than normal. This cannot be considered as resistance for the drug.

As we know estrogen plays a major role in controlling the vulvovaginal environment. Estrogen increases glycogen content of vaginal epithelium. This acts as the substrate for lactobacilli. Lactobacilli converts glycogen into lactic acid resulting in vaginal acidity reaching a pH of 4.5. This acidity acts like the first line of defense in protection of the environment. Normal vaginal flora is a mixture of organisms such as *E. coli, Group B strep, Mycoplasma genitalis, Gardnarella vaginalis and Candida albicans*. In estrogen depleted environments, infections from yeast and bacterial vaginosis is less common[7,8].

There are several species belonging to Candida, of which the most common species belongs to *Candida albicans*. Other sub species belonging to Candida are *C. glabarata, C. krusei, C. tropicalis, C. parapsilosis*. Another species not belonging to Candida but is a member of this fungal pathogenic group is *Saccharomyces cerevisiae*.

Most women experience at least one episode of candida infection during their lifetime[9] (BASHH Guideline 2019). 75% of women will have at least one episode of VVC in their lifetime, and 40-45% will have two or more episodes[9]. Studies have reported that approximately 6% of women of reproductive age will develop recurrent disease[10,12]. A large survey across five European countries and the US found that over 20% of women reporting at least one episode of vaginal yeast infection also reported a 12-month period with four/more infections. The probability of developing recurrent VVC after an initial infection was 10% by the age of 25 years and 25% by the age of 50 years[13].

Common symptoms of vulvovaginal candidiasis are itching, burning, oedema, urinary symptoms, pain during intercourse and abnormal discharge. However, a significant proportion are asymptomatic. It should be less common in prepubertal girls and women after menopause. But VVC is often overdiagnosed[14]. It is said that on membranes other than the vagina, IL-17 mediated immunity may play a crucial factor[15]. Although there is a relationship between women with allergy and atopy observed to be suffering more from VVC, the cause for that is not correctly identified as whether it is due to patient factor or the use of steroids.

There are common risk factors know for recurrent VVC. They are mostly host related factors rather than virulence or reintroduction[16]. Host factors considered important are:

1. Poorly controlled diabetes
2. Estrogen use or endogenous estrogen (pregnancy, Hormone Replacement Therapy, Oral Contraceptive Pills.)
3. Antibiotic use
4. Persistence of candida genome.

Iron deficiency, anemia and recurrent VVC has shown a link. However, it is a possibility rather than a foregone conclusion[17].

A lectin known as Mannose Binding Lectin (MBL) of which the deficiency has shown a link to immunity in several research articles have shown that the polymorphism of codon 54 is associated with recurrent and acute VVC. It is said that once with MBL variant allele, heterozygous genotype makes women more susceptible to VVC than their normal controls. This is further evident in the study of the homozygotic genotype[18,19].

History

Apart from presenting symptoms, specifically looking for information regarding the vulva, vagina and anus is useful. Understanding duration and taking treatment during such times is vital in planning out management. Specific questions on sexual history, hygiene practices, attempted treatment by the patient herself, as well as the medical conditions of the woman and the partner (diabetes, HIV, IBD) are important. Last but not the least, the relationship between the symptoms, the menstrual cycle and sexual activity is important in tailoring the treatment.

Common clinical features are

- itching
- discharge, (non-offensive or curd-smelling)
- soreness

- dyspareunia
- cyclical symptoms
- redness
- cracks
- oedema
- evidence of excoriations
- involvement of other mucus membranes (should arouse suspicion of problems of immunity)

Examination

Thorough vulvovaginal examination and detailed documentation of the appearance of the vulva, intercrural folds, anus and perineum is important. In cases of recurrent longstanding problems, photographic documentation of the pretreatment status *with patient consent is very helpful.*

Of the differential diagnosis of inflammatory conditions, it is good to know that *Gardnerella vaginalis* does not affect the vulva and is not an inflammatory condition. However, candidiasis and trichomoniasis may lead to inflammation, erythema and edema of vulva in addition to the condition of the vagina and the cervix. Of the inflammatory conditions of infectious nature, fissuring is usually associated with vaginal candidiasis[20].

In dealing with possible VVC patients, emphasis should be paid to being very gentle on speculum examination as the vulva could be sore. Samples of discharge should be collected from the fornices and vaginal wall. The collected samples for pH testing should be from the mid-vagina as cervical mucus, semen or lubricants from the fornix could give false readings on pH.

Tests for diagnosis

Clinical diagnosis by typical features is usually sufficient for first time diagnosis and initiation of treatment though confirmation by laboratory sample is ideal.
Macroscopy and microscopy are the main diagnostic tools for vaginal candidiasis. pH testing, KOH whiff test (smell test) would give clues in the direction of diagnosis.

Table 1 below compares and contrasts normal physiological discharge from Candida vulvovaginitis.

Table 1.

Condition	Symptoms	Physical Exam Findings	pH	Microscopic Test results	Diagnostic Tests
Normal physiological discharge	White and creamy or clear discharge	White colored discharge in vaginal fornix and walls	3.5 - 4.5	Mature squamous cells, rare PMN, background bacteria dominated by lactobacillus	N/A
Candida vulvovaginitis	Normal appearing discharge or white, thick discharge, Burning Pruritus Dyspareunia Dysuria	White, thick curd-like, vaginal discharge; Present in Severe CVV, Erythema, excoriations, oedema and fissures can be present.	3.5 - 4.5	Branching pseudohyphae, budding pseudohyphae (10x), or spores (40x) with 10% potassium hydroxide. Mature squamous cells, rare PMNs, bacteria dominated by lactobacillus	Recommended: Microscopy Yeast culture Alternative: FDA-approved commercial tests

Commercially available kits are rarely used for diagnosis of Gardnerella vaginosis.

In microscopy by gram stain or use of phase contrast wet film, the clues pointing towards candidiasis are, detection of pseudohyphae or spores. Absence of pseudohyphae is indicative of infection with *C. glabarata*. Presence of neutrophils points towards inflammation. (Presence of candida without neutrophils is suggestive of colonization rather than inflammation).

Fungal culture for Candida is needed for tricky situations[21]. With modern microscopy the detection is in the range of 50-70% but a substantial number of cases are missed. Mixed infections by *C. albicans* and other species could be found in recurrent VVC or in people with poor response to therapy. In such cases, detailed sensitivity check of antifungal agents would be necessary. Commonly used self-treatments make sensitivity of the microscopy lower than expected. With a high degree of clinical suspicion with negative microscopy, resorting to culture remains an option. Up to 90% infections could be detected by this method. About 90% of candida isolated in this manner are sensitive to commonly used azoles and oral fluconazole [21,22]. Drawback in culture as a method of diagnosis mostly due to the delay in reading culture hence the diagnosis. The culture is useful for diagnosis of *Candida glabarata*, which may be difficult to recognize on microscopy as it produces blastospores not pseudohyphae as in *Candida albicans*. The culture is reported to be positive for 30% of asymptomatic women at a given time[23]. Hence clinical correlation is very important before treatment.

Newer methods using PCR that yield results in a few hours are commercially available and have a sensitivity and a specificity of 97.7 and 93.2 % respectively[24]. These tests are expensive. PCR does not recognize sub species of candida. Newer PCR technology is available for detection of other sub species such as *Candida albicans, tropicalis, parapsiliosis, glabarata, krusersi*.

ACOG (Practice bulletin #215) classify vulvovaginal candidiasis into uncomplicated candidiasis and complicated candidiasis. The patients with uncomplicated candidiasis have infrequent episodes, mild to moderate symptoms, *Candida albicans* infection and normal immunity status. The complicated candidiasis is described as recurrent episodes, (more than 4 or more episodes per year) severe symptoms, non-albicans candidiasis, immunocompromised or immunosuppressed or presence of diabetes.

Management

As in any infection, general advice on VVC are:

- Avoid irritants such as soaps/moisturizers with perfume.
- Use of mild moisturizer/emollient in place of soap to act as a cleanser, skin barrier, and moisturizer.
- Wearing underwear made of breathable fabric.

Hygienic practices below have been shown to be weakly associated with increased recurrent VVC and may be explored in patients with recurrent VVC:

- Use of excessively fitted/non air permeable underwear
- Use of intermenstrual pantiliners
- Vaginal douching [25, 26, 27, 28].

There is no necessity to avoid sexual activity for medical reasons. However, most women try to avoid sexual activity due to discomfort.

Psychosexual issues associated with chronic VVC should be a fact to remember in managing patients. Additional investigations are in the direction of blood sugar assessment, Glucose Tolerance Test for detection of renal glycosuria, blood testing for detection of anemia, screening for Mannose Binding Lectin and investigations for immune disorders when indicated.

Treatment

Treatment of VVC is simple. In women who are not married, the drug of choice is fluconazole. It is 150mg single dose orally for acute non-recurrent VVC. In women who have a history of sexual intercourse, topical treatment with clotrimazole vaginal pessary 500mg as a single dose is the drug of choice. There have not been any data to support superiority over topical over oral for the treatment of acute VVC[29,30]. Vaginal imidazoles and oral azoles give satisfactory cure of more than 80% in acute VVC[29,33]. One randomized controlled trial[31] has shown oral fluconazole to be more effective than longer courses of clotrimazole 200mg for 7 days from the start of treatment.

In pregnancy topical treatment is advised as the first line treatment for acute VVC. There is very little absorption of imidazoles from the vagina. Hence rarity

of any systemic side effects. Recommended treatment in pregnancy is clotrimazole 500mg pessary intravaginally at night up to 7 nights. With regard to pregnancy, longer courses are recommended as in a systematic review; where a 4 day course with a cure rate of 50% was studied against a seven-day course with a cure rate of 90%[32]. In a systematic review in the use of fluconazole even in the first trimester, the drug was not shown to increase overall risk of congenital malformations but may have shown a possible link with Tetralogy of Fallot. A study by the US National Birth Defects Prevention Study by Center of Disease Control (NBDPS) found an association of fluconazole with cleft lip and palate and the transposition of great arteries. However, the use of fluconazole in the study was very low[34]. In view of these studies, the use of fluconazole in the latter part of the pregnancy does not seem to have an effect on the wellbeing of the fetus[35].

A large study from >1.5 million pregnancies in Sweden and Norway compared pregnancies exposed and not exposed to fluconazole and showed no significant difference in risk of stillbirth or neonatal death when exposed to either high (>300mg) or low doses of fluconazole. The results were published online 12th June 2018 in the Journal of American Medical Association. However, SLCOG would like to remind clinicians that the FDA cautions the use of fluconazole due to increased risk of miscarriage though it is small. Therefore SLCOG would recommend first time use of local therapy and reserving oral fluconazole therapy for complicated and complex cases and in such situations also to avoid its use before 16th week of pregnancy. (However, 4% of American women are known to use fluconazole for vulvovaginal candidiasis without knowing of the pregnancy themselves).

Concentration of fluconazole in breast milk is very low.

It is of note that fluconazole is a moderate inhibitor of cytochrome 450 isoenzyme 2C9 and CYP 3A4. This effect lasts about 4 -5 days after the end of fluconazole treatment as the drug has a long half-life. It must be kept in mind that fluconazole is associated with prolongation of the QT interval in ECG. Therefore, before prescription, clinician must avoid use of any other drug which has the same effect. Also, the status of hypokalemia which could intensify the effect should be kept in mind. Commonly used drugs that have the same effect is erythromycin and astemizole (a second-generation antihistamine).

In severe cases of VVC oral treatment of fluconazole on day 1 and day 4 is recommended. As an alternative to this vaginal use of clotrimazole 500 mg pessary on day 1 and 4 or miconazole vaginal 1200 mg on day 1 and day 4 is recommended. In the presence of severe symptoms, tissue inflammation, oedema and fissuring, unless contraindicated, fluconazole use on day 1 and day 5 is recommended. Low potency steroid creams and topical application of antifungal creams could give rapid relief of symptoms arising from the external vulvar skin.

In recurrent VVC, a regimen of fluconazole every 72 hours for 3 doses followed by a maintenance dose of 150mg orally once a week for 6 months is recommended by BASHH Guideline 2019. Alternative to this, topical imidazole therapy, use for 7 to 10 days at the beginning followed by clotrimazole 500mg intravaginally once a week for 6 months could be considered. Itraconazole 50 to 100mg could be used for maintenance therapy. However, this therapy should not be considered in pregnancy or for women at risk of getting pregnant. Two randomized trials on fluconazole for recurrent VVC as given in the guideline have been shown to achieve clinical remission in 82-90% of cases[36].

If the patient relapses between weekly treatment, consider twice weekly treatment. The available literature does not support low dose long regimens of fluconazole (50mg every other day for 28 days)[37]. Oral azoles have a low risk of drug induced idiosyncratic hepatitis. Fluconazole is less frequently associated with this than itraconazole.

In patients with recurrent VVC with poor or partial response to therapy, consideration should be given to identify non-*albicans* species with resistance to common azoles. Treatment should then be based on available drug sensitivity patterns. Commonly available drugs for azole resistance use are nystatin pessaries 100000 units vaginally nightly/nocte daily for 2 weeks. Other drugs for such use are

- Boric acid vaginal suppositories 600mg for 14 days (avoid pregnancy or risk of pregnancy)
- Amphotericin B vaginal suppositories 50mg once a day for 14 days, flucytosine 5g cream or 1g pessary vaginally combined with amphotericin or nystatin for 14 days.

For maintenance of such cases nystatin pessaries for 14 days every month for 6 months or alternative regimes of 14 days a month for 6 months could be considered.

Of the non-*albicans* species, *C. glabarata*, though susceptible to azoles, have elevated MICs. Therefore, poor response is noted with standard treatment. *Candida krusei* is resistant to fluconazole intrinsically.

Nystatin preparations are well tolerated and coated to give a 70-90% cure rate in acute VVC[38,39]. Boric acid is considered safe and effective other than in pregnancy, and in cases of mucosal irritation, the dose has to be reduced by half. Amphotericin in this context has shown to be 70% success[40].

Intravaginal preparations could damage the latex of condoms hence accidental pregnancy could be cause for concern.

Alternative treatments, antiallergic medication in the form of antihistamines and montelukast could offer some relief to women with concomitant atopy which could be triggered by VVC. However, no scientific benefit has been shown in the use of probiotics, yogurt and honey. Diabetes mellitus is a known trigger of VVC be it acute or recurrent. Hence good control of diabetes is recommended for women with VVC.

HIV infection if not controlled properly, is a cause for VVC and recommendation is for proper control of HIV. Use of hormones with estrogen is a cause for VVC and the clinician should be aware of this.

The use of intrauterine contraceptive devices and its association with recurrent VVC is very weak. However, in the absence of any alternative for management of recurrent VVC in the presence of either copper or LNG IUS, removal of such device with provision of another form of contraception could be the answer. The effect of progesterone only method on candidiasis, in theory, should be favorable. However systematic review quoted[41] could not come to a conclusion on the effect of progesterone only contraception and recurrent VVC.

Follow up is recommended for people with recurrent VVC especially if the initial response is partial or poor. They should be advised to seek specialized treatment even on follow up if their symptoms recur.

There is no scientific data to support treatment of asymptomatic male sexual partners in VVC. However, symptomatic male partners need to be treated[42,43].

References

1. ACOG. Vaginitis in Nonpregnant patients. ACOG Practice Bulletin No. 215. Obstet Gynecol VOL. 135, No. 1, January 2020.
2. Wang FJ, Zhang D, Liu ZH, et al. Species Distribution and In Vitro Antifungal Susceptibility of Vulvovaginal Candida Isolates in China. Chin Med J (Engl) 2016; 129(10): 1161-5.
3. Bulik CC, Sobel JD, Nailor MD. Susceptibility profile of vaginal isolates of *Candida albicans* prior to and following fluconazole introduction - impact of two decades. Mycoses 2011; 54(1): 34-8.
4. Araj GF, Asmar RG, Avedissian AZ. Candida profiles and antifungal resistance evolution over a decade in Lebanon. J Infect Dev Ctries 2015; 9(9): 997-1003.
5. Guerrero-Lozano I, Aznar-Marin P, Garcia-Agudo, L, et al. 4. Vulvovaginal candidosis by non-*albicans Candida* species. Mycoses 2012; 55(Suppl4): 95-338.
6. Hetticarachchi N, Ashbee HR, Wilson JD. Prevalence and management of non-*albicans* vaginal candidiasis. Sex Transm Infect 2010; 86(20): 99-100.
7. Tartaglia E, Giugliano B, Ucciferri C, Giannattasio A, Giuliano P, Iannaccone VL, et al. Vulvo-vaginitis in prepubertal girls: new ways of administering old drugs. J Pediatr Adolesc Gynecol 2013; 26: 277-80.
8. Zuckerman A, Romano M. Clinical recommendation: vulvovaginitis. J Pediatr Adolesc Gynecol 2016; 29: 673-9. (Systematic Review).
9. Foxman B, Muraglia R, Dietz JP, Sobel JD, Wagner J. Prevalence of recurrent vulvovaginal candidiasis in 5 European countries and the United States: results from an internet panel survey. J Low Genit Tract Dis 2013; 17: 340-5.
10. Hurley R, De Louvois J. Candida vaginitis. Postgrad Med J 1979; 55: 645-47.
11. Denning DW, Kneale M, Sobel JD, et al. Global burden of recurrent vulvovaginal candidiasis: a systematic review. Lancet Inf Dis 2018 Nov; 18: e339-e347.

12. Hurley R. Recurrent Candida infection. Clin Obstet Gynaecol 1981; 8(1): 209-14.

13. Foxman B, Muraglia R, Dietz JP, et al. Prevalence of recurrent vulvovaginal candidiasis in 5 European countries and the United States: Results from an internet panel survey. J Low Genit Tract Dis 2013; 17(3): 340-5.

14. Tibaldi C, Cappello N, Latino MA, Masuelli G, Marini S, Benedetto C. Vaginal and endocervical microorganisms in symptomatic and asymptomatic non-pregnant females: risk factors and rates of occurrence. Clin Microbiol Infect 2009; 15: 670-9.

15. Yano J, Kolls JK, Happel KI, et al. The Acute Neutrophil Response Mediated by S100 Alarmins during Vaginal Candida Infections is Independent of the Th17-Pathway. PLoS ONE 2012; 7(9): e46311.

16. Fidel PL, Jr., Sobel JD. Immunopathogenesis of recurrent vulvovaginal candidiasis. Clin Microbiol Rev 1996; 9(3): 335-48.

17. Naderi N, Etaati Z, Rezvani Joibari M, et al. Immune deviation in recurrent vulvovaginal candidiasis: Correlation with Iron Deficiency Anemia. Iran J Immunol 2013; 10(2): 118-26.

18. Henic E, Thiel S, Mårdh PA. Mannan-binding lectin in women with a history of recurrent vulvovaginal candidiasis. Eur J Obstet Gynecol Reprod Biol 2010; 148(2): 163-5.

19. Nedovic B, Posteraro B, Leoncini E, et al. Mannose-binding lectin codon 54 gene polymorphism and vulvovaginal candidiasis: a systematic review and meta-analysis. Biomed Res Int 2014: 738298-99.

20. Edwards L. Vulvar fissures: causes and therapy. Dermatol Ther 2004; 17: 111-6.

21. Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines, 2015. Centers for Disease Control and Prevention [published erratum appears in MMWR Recomm Rep. 2015; 64:924]. MMWR Recomm Rep 2015; 64(RR-03): 1-137.

22. Sobel JD. Vulvovaginal candidosis. Lancet 2007; 369: 1961-71.

23. Nyirjesy P. Management of persistent vaginitis. Obstet Gynecol 2014; 124: 1135-46.

24. Cartwright CP, Lembke BD, Ramachandran K, Body BA, Nye MB, Rivers CA, et al. Comparison of nucleic acid amplification assays with BD affirm VPIII for diagnosis of vaginitis in symptomatic women. J Clin Microbiol 2013; 51: 3694-9.

25. Ekpenyong CE, Inyang-etoh EC, Ettebong EO, et al. Recurrent vulvovaginal candidosis among young women in south eastern Nigeria: The role of lifestyle and health-care practices. Int J STD AIDS 2012; 23(10): 704-9.

26. Jankovic S, Bojovic D, Vukadinovic D, et al. Risk factors for recurrent vulvovaginal candidiasis. Vojnosanit Pregl 2010; 67(10): 819-24.

27. Shaaban OM, Abbas AM, Moharram AM, et al. Does vaginal douching affect the type of candidal vulvovaginal infection? Med Mycol 2015; 53(8): 817-27.

28. Heng LS, Yatsuya H, Morita S, et al. Vaginal douching in Cambodian women: its prevalence and association with vaginal candidiasis. J Epidemiol 2010; 20(1): 70-6.

29. Nurbhai M, Grimshaw J, Watson M, et al. Oral versus intra-vaginal imidazole and triazole anti-fungal treatment of uncomplicated vulvovaginal candidiasis (thrush). Cochrane Database Syst Rev 2007; 4: CD002845.

30. Sekhavat L, Tabatabaii A, Tezerjani FZ. Oral fluconazole 150 mg single dose versus intra-vaginal clotrimazole treatment of acute vulvovaginal candidiasis. J Infect Public Health 2011; 4(4): 195-9.

31. Lopez M, Ester J. Candidiasis (vulvovaginal). BMJ Clin Evid 2015: 0815.

32. Young GL, Jewell D. Topical treatment for vaginal candidiasis (thrush) in pregnancy. Cochrane Database Syst Rev. 2001; (4): CD000225.

33. Watson MC, Grimshaw JM, Bond CM, et al. Oral versus intra-vaginal imidazole and triazole anti-fungal treatment of uncomplicated vulvovaginal candidiasis (thrush): a systematic review. Int J Gynaecol Obstet 2002; 109(1): 85-95.

34. Howley MM, Carter TC, Browne ML, et al. Fluconazole use and birth defects in the National Birth Defects Prevention Study. Am J Obstet Gynecol 2016; 214(5): 657.

35. Medscape Medical News, June 12. 2018. Oral Fluconazole for Thrush in Pregnancy Doesn't Up Stillbirth. https://www.medscape.com/viewarticle/897935

36. Rosa MI, Silva BR, Pires PS, et al. Weekly fluconazole therapy for recurrent vulvovaginal candidiasis: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol 2013; 67(2): 132-6.

37. Perlin DS, Shor E, Zhao Y. Update on antifungal drug resistance. Curr Clin Microbiol Rep. 2015; 2: 84-95.

38. Odds FC. Candida and Candidosis; A review and bibliography. Second ed. London: Bailliere Tindall; 1988.

39. Dressen G, Kusche W, Neumeister C, et al. Diagnosis of vulvovaginal Candidiasis and effectiveness of combined topical treatment with nystatin: Results of a non-interventional study in 973 patients. Open Womens Health J 2012; 6: 19-23.

40. Spacek J, Buchta V, Jílek P, et al. Clinical aspects and luteal phase assessment in patients with recurrent vulvovaginal candidiasis. Eur J Obstet Gynecol Reprod Biol 2007; 131(2): 198-202.

41. van de Wijgert JH, Verwijs MC, Turner AN, et al. Hormonal contraception decreases bacterial vaginosis but oral contraception may increase candidiasis: implications for HIV transmission. AIDS 2013; 27(13): 2141-53.

42. Bisschop MP, Merkus JM, Scheygrond H, et al. Co-treatment of the male partner in vaginal candidosis: a double-blind randomized control study. BJOG 1986; 93(1): 79-81.

43. Spence, D. Candidiasis (Vulvovaginal). BMJ Clin Evid 2010 5; 2010.