Literature Review

Management of Vulvovaginal Candidiasis in Pregnancy

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Abstract

Objective: This study aimed at describing VVC therapy that has been proven to be safe in pregnancy.

Background: Pregnancy is a risk factor for vulvovaginal candidiasis (VVC). The most common cause of VVC in pregnancy is *Candida albicans.* When symptoms and signs of vulvar pruritus, pain, swelling, redness, burning sensation, dyspareunia, dysuria, vulvar edema, fissures, excoriation and vaginal discharge are found which suggest VVC, it is necessary to perform microscopic examination and/or fungal culture to establish the diagnosis of VVC. In pregnancy, VVC must be treated as soon as possible because it can cause adverse perinatal outcomes such as premature labor, premature rupture of membranes, low birth weight babies and fetal brain problems. Unfortunately, prescription oral antifungal therapy in pregnancy is still found. Treatment with oral antifungal is not recommended because of the risk of causing congenital abnormalities in the fetus.

Methods: Literatures in English and Indonesian were searched with topic restrictions on the type of publication for the last thirty years.

Summary: Topical intravaginal antifungal therapy such as clotrimazole and nystatin, are the recommended treatment for VVC in pregnancy that has been shown its safety. In addition, giving prophylaxis in the last trimester of pregnancy in asymptomatic VVC cases provides good pregnancy and neonatal outcomes but is still debated. In severe, prolonged or recurrent cases of VVC, other co-infections may be sought which may also need to be managed. Administration of probiotics for VVC therapy still requires further research.

Keywords: Candidiasis, Clotrimazole, Nystatin, Pregnancy, Topical

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INTRODUCTION

Vulvovaginal candidiasis (VVC) is defined as *Candida* infection of the vagina and vestibule which can extend to the labia minora, labia majora, intercrural and perianal.[1,2] VVC is one of the most common causes of vulvovaginal itching and vaginal discharge.[3] After bacterial vaginosis, VVC is the second most common cause of vaginitis.[2] At least 70-75% of women of childbearing age have experienced symptomatic VVC once during their life and 40-50% have one reinfection.[3,4] As many as 5-8% have recurrent infections (VVC ≥3 episodes per year).[3,5]

Healthy women may experience VVC sporadically.6 However, the infection is often associated with host-related factors and changes in the vaginal environment including pregnancy.[6,7] The risk of developing VVC in healthy women is 20% and higher in pregnancy (30-50%).[4,8] This is related to physiological changes in pregnancy.[3,5] Because there is an increased risk of VVC in pregnancy, early detection and management must be performed immediately so that the poor outcomes in pregnancy and the fetus can be prevented.

Several antifungal therapy options for VVC are available in Indonesia. It is important to know

that the use of antifungals in pregnancy must be administered with caution and the appropriate form chosen. The recommended antifungal treatment in pregnancy is topical antifungal, while oral antifungal is not recommended because of the risk of causing congenital abnormalities in the fetus. However, it cannot be denied that oral antifungal therapy in pregnancy is still found. In Indonesia, there is no literature review that specifically discusses about VVC therapy in pregnancy.

This literature review aims to describe VVC therapy that has been proven to be safe in pregnancy based on the correct diagnosis of VVC. Literature searching in English and Indonesian with topic restrictions on the type of publication for the last thirty years was performed, sourced from PubMed-MEDLINE, Google Scholar, university databases, electronic journals, electronic books, and official health organization websites. Hopefully, this literature review can be a guidance for providing safe VVC therapy in pregnancy.

LITERATURE REVIEW

Prevalence of Vulvovaginal Candidiasis in Pregnancy

In a meta-analysis study in Africa, the prevalence of VVC in pregnancy was 29.2% of 4,185 pregnant women subjects.[9] In other studies, the prevalence of VVC in pregnancy was reported from Lebanon, Jamaica, Argentina and China respectively 44.8%, 30,7%, 25% and 21,8%.[10-13] The species of *Candida* that causes most VVC in pregnancy is *Candida albicans.* However, other species have also been reported, such as *Candida glabrata, C.krusei, C.tropicalis,* and *C.parapsilosis* (table 1).

Table 1. Candida species cause Vulvovaginal Candidiasis in Pregnancy

Author, Country, year	Percentage of Candida Species					
	C. albicans	***C. glabrata***	***C. krusei***	***C. tropicalis***	***C. parapsilosis***	**Others**
Farr A *et al,* Austria, 2021[1]	92.4	3.8	1.9			1.9
Ghaddar *et al,* Lebanon, 2020[14]	42	41	17			
Tsega *et al,* Etiopia, 2019[15]	56.25.	17.7	21.9	1		3.1
Mushi MF *et al,* Tanzania, 2019[16]	63.4	16.8		17.8		
Zhai *et al,* Cina, 2018[13]	79.8	13.5	2.2	1.1	3.7	

Pathophysiology of Vulvovaginal Candidiasis in Pregnancy

One-third of pregnant women have at least once experienced VVC during pregnancy.[17] Change of *Candida* yeast cell into hyphae (pathogen) can occur during changes in the physiology of pregnancy.[18] The increased risk of VVC and asymptomatic colonization in pregnancy may be due to pregnancy-related factors, namely increased levels of estrogen, lower vaginal pH, increased production of vaginal mucosal glycogen and immunological changes.[3,5]

Increased estrogen facilitates adhesion and penetration of yeast to vaginal mucosal epithelial cells.[5,17] Estrogen also promotes the hyphal formation and elaboration of enzymes (such as Secreted Aspartyl Proteinase) that enhance *Candida* colonization.[5] The lower vaginal pH during pregnancy also increases yeast adhesion in the vaginal mucosa.[4] Increased glycogen creates an optimal environment for the development of *Candida*.[17] Glycogen metabolism in *C. albicans* contributes to the restoration of its survival and virulence in the host.[19] Immunological changes during pregnancy may contribute to the severity and susceptibility to infection during pregnancy.[5] The anti-inflammatory state from the second trimester of pregnancy until delivery results in a weaker local genital immune response to *Candida* so that although colonization frequency increases, symptoms are less pronounced.[5]

Vulvovaginal Candidiasis and Perinatal Outcomes

VVC in pregnancy can cause extensive inflammation, which affects perinatal outcomes.[20] Fungal infections of the female genital tract cause inflammation and increase proinflammatory mediators in vaginal fluids, such as interleukin-8, resulting in cervical ripening and contractions which are associated with preterm birth.20 These outcomes are associated with inflammation in pregnancy in symptomatic VVC.[20]

In one study, it was reported that 35% of patients with preterm labor were infected with *C. albicans*. Out of 12 pregnant women with premature rupture of membranes, 4 mothers (33.3%) showed positive results for *C. albicans* infection. Among 29 mothers who had low birth weight babies, 5 (17.2%) were positively infected with *C. albicans.* Of the 40 pregnant women who gave birth prematurely, 14 (35%) were positive for *C. albicans.*[21] However, the results of this study when associated with VVC in pregnancy were not statistically significant.[21] Likewise in a meta-analysis study on various perinatal outcomes related to VVC in pregnancy was not significant.[21] Factors that influence the results are different specimen collection times (if it was taken from pregnant women in the late trimester, it is unlikely to affect the occurrence of premature labor), the diagnostic were performed only on the lower genital tract (otherwise, upper genital tract infection is an early sign of preterm labor) and the different methods of diagnosis were used in the studies included in the studies (there could be misclassification resulting in no association in this meta-analysis).[21]

It has been reported in other studies that VVC in pregnancy and infected fetus is directly associated with an increased risk of childhood epilepsy.[22] Although the mechanism is not fully understood, it is possible that cytokines produced by the immune system during infection in pregnancy may harm the developing brain of fetus.[22,23] High concentrations of certain cytokines in amniotic fluid and neonatal blood have been associated with cerebral palsy.[23] The association between VVC in pregnancy and the risk of epilepsy for children born in the first 3 years of life from mothers who experience VVC during pregnancy (especially in the second trimester), the born children 2.79 times at risk of experiencing epilepsy (only in children born prematurely).[23] These various outcomes remind us of the importance of screening for infection during antenatal examinations to prevent VVC from expanding or ascending so that unwanted perinatal outcomes can be prevented.[24]

Clinical Manifestations and Diagnosis of Vulvovaginal Candidiasis

From a clinical perspective, it is necessary to distinguish between complicated and uncomplicated VVC cases related to management.[1,4] VVC in pregnancy is included in the complicated classification.[4] VVC clinical manifestations are vulvar pruritus, pain, swelling, erythema, burning, dyspareunia and dysuria.[1,25] The signs include vulvar edema, fissures, excoriation and vaginal discharge (thick or watery like curd, odorless).[1,25,26] The diagnosis is based on clinical and mycological laboratory test (microscopic examination and/or fungal culture).[25]

On a direct microscopic examination with saline or 10% potassium hydroxide from vaginal secretion specimens, fungal elements (yeast, budding yeast, hyphae or pseudohyphae) can be found using 400x magnification (10x ocular lens plus 40x objective lens).[1,25] In fungal cultures, yeast colonies can grow.[25] The media used for culturing *Candida* spp. are Sabouraud Dextrose Agar and parallel with Chromogenic Agar with its pigmentation ability to differentiate *Candida*.[1] In vitro antifungal sensitivity test is needed, especially in cases of chronic VVC due to *Candida* non-albicans.[1] To get accurate results, it is important to pay attention to how to obtain vaginal secretion specimens, namely: the correct way to take specimens, the amount is adequate, the sterility of the tools (sterile swab and 0.9% NaCl in a sterile closed tube) and safe-fast transport of specimens to the laboratory.[27]

The direct microscopic examination should be performed for all women with symptoms or signs of VVC. If the results are positive, treatment should be performed.[25] Fungal elements can be found by microscopy in 50-80% of VVC.[1] If the test results are negative but there are signs and symptoms of VVC, it is recommended to have fungal cultures from vaginal secretion specimens.[25] Fungal cultures are needed for unclear cases.[1] No fungal elements were found on microscopic examination possibly because the number of microorganisms is very small, thereby reducing the sensitivity of the examination.[1] Even

though the fungal burden is low, this condition still can trigger inflammation and therefore fungal cultures should be performed for species identification in some cases, for example in patients with recurrent chronic VVC.[1]

In 90% of VVC cases, itching is the dominant symptom.[1] But not all itching complaints must be VVC, only 35-40% of itching complaints are actually caused by VVC.[1] In one study, clinical findings of maceration of the vulva and white, curd-like vaginal discharge had a good diagnostic accuracy with PPV values 58% and 100% respectively.[26] These clinical signs can be a characteristic to direct us to VVC.[26] There is no evidence that VVC symptoms in pregnancy are more severe than in non-pregnant condition, but the VVC adds discomfort to pregnancy, especially recurrent VVC.[5]

In reality, microscopic examination or culture is not always possible to perform.[1] In these conditions, empirical treatment may be considered.[25] However, identifying *Candida* spp. without any signs and symptoms of VVC, is not an indication for treatment because around 10% -20% of women experience *Candida* colonization in the vagina.[25]

Serological assay is not used in diagnosing VVC because antibody levels can be detected in women with and without VVC (e.g. intestinal colonization).[1] Most PCR tests for yeast are not FDA-approved.[25] Fungal culture tests remain the gold standard for diagnosing VVC.[25]

Vulvovaginal Candidiasis Therapy in Pregnancy

Given the risk of teratogenesis during pregnancy, prescribing antifungal drugs during this period must be cautious.[28] A systematic review of congenital malformations and use of fluconazole during the first trimester of pregnancy found that women who have fluconazole during pregnancy was 1.29 times the risk of developing cardiac abnormalities.[3] The association between fluconazole treatment during pregnancy and the risk of malformations in the fetus in 40,000 mothers and babies in case-control study was found that the use of fluconazole during pregnancy has a risk of causing not only labioschisis and/ or palatoschisis but also dextro-transposition of the great arteries 5.53 times and 7.56 times respectively.[3] A cumulative dose of fluconazole 150-6,000 mg given during the first trimester of pregnancy, has been associated with a 3.16 times increased risk of significant fetal tetralogy of fallot, according to study in Denmark.[1]

Fluconazole use during pregnancy was also associated with spontaneous abortion, although there was no increased risk if consuming fluconazole before pregnancy or using a topical azole class.[3] Studies of other oral antifungal therapies such as itraconazole, ketoconazole and voriconazole have been associated with various outcomes, such as abortion, fetal musculoskeletal malformations (in experimental animals) and fetal skeletal-visceral abnormalities (in experimental animals).[28] Current guidelines state that oral antifungal therapy should be avoided and only topical antifungal therapy can be used to treat VVC in pregnancy.[1,2,3]

Several studies have reported a significant reduction in preterm birth following intravaginal clotrimazole treatment in cases of VVC during the first trimester of pregnancy.[1] Treatment of VVC in pregnancy with topical clotrimazole during the first trimester, can prevent fetal malformations and miscarriage.[1] In a study in Australia, a trend toward decreased preterm birth was shown after clotrimazole treatment in the first trimester.[1] Another study reported an increase in preterm birth rates after recurrent asymptomatic colonization with *Candida* in early pregnancy.[1]

According to the British Association of Sexual Health and HIV, treatment of asymptomatic CCV is not given due to the colonization of *Candida* spp. not associated with preterm labor and low birth weight.[2] In contrast, prophylaxis is recommended during the third trimester of pregnancy to reduce the rate of neonatal candidiasis, particularly oral candidiasis and diaper dermatitis.[1,2] Term neonates are more likely to develop oral candidiasis or diaper dermatitis during the first year of life in pregnant women who experience *Candida* colonization through mother-to-neonatal transmission during vaginal delivery.[1] Therefore, prophylactic antifungal treatment may be recommended in cases with asymptomatic colonization during the last weeks of pregnancy to prevent transmission to newborns in vaginal delivery.[1] Prophylaxis administration significantly reduced the risk of oral candidiasis and diaper dermatitis from 10% to 2% at 4 weeks of life.[1] The association of asymptomatic *Candida* spp. colonization and perinatal outcome remains unclear.[2] The fact that treatment with topical clotrimazole during the first trimester of pregnancy has been shown to reduce preterm birth rates warrants further

prospective study.[2,4]

Topical azole therapy can be used at all stages of pregnancy because of minimal systemic exposure to treatment by intravaginal administration.[4,28] The Food and Drug Administration (FDA) has assigned topical clotrimazole as pregnancy category B agents.[28] Imidazoles and other topical triazoles have been approved by the FDA as pregnancy category C.[4,28] Several clinical trials confirmed the safety of clotrimazole in pregnancy.[4] There is no association between intravaginal clotrimazole treatment with congenital abnormalities.[4] 55,64 55, 55 67

Treatment of VVC in pregnancy with clotrimazole 100 mg (vaginal tablet), administered for approximately 1 week, has a high cure rate (78-88%).[4] Similar results were obtained with application of clotrimazole 1% vaginal cream for 1 week.[4] Intravaginal clotrimazole was significantly more effective than placebo treatment.[4] Treatment of VVC with clotrimazole 500 mg vaginal tablets or vaginal cream was as effective as administration of fluconazole 150 mg orally in a single dose.[1] Comparison of the use of a single dose of clotrimazole 500 mg decreased the effectiveness of treatment compared to clotrimazole 200 mg for 3 days.[4]

Topical nystatin is an alternative treatment that has been extensively studied for administration in the first trimester of pregnancy.[29] No risk associated with major malformations has been observed in multiple studies.[29] According to the FDA, nystatin include in the A category for pregnancy used.[28] The dose of nystatin recommended during pregnancy is 100,000 IU intravaginally once daily for 14 days.[1,29] Nystatin is recommended as an alternative therapy for *Candida* non-albicans.[30] In European guidelines, nystatin is used as a first-line treatment of chronic VVC due to *C. glabrata.*[30] However, for all *Candida* species, nystatin's antifungal activity is also effective.[30]

Tabel 2. List of Intravaginal Topical Antifungals

Topical (Intravaginal) Antifungals	Dosage	Medicinal Preparations	Duration of drug administration (days)	Availability in Indonesia	FDA Category for Pregnant Women
Nistatin	100.000 IU[1]	100.000 IU vaginal tablet	14	Available *	A[28]
	200.000 IU[1]		6		
Klotrimazol	1 x 100mg[4]	100mg vaginal tablet	7	Available **	B[28]
	1 x 200mg[1]		3		
	1 x 500mg[1]	500mg vaginal tablet	1	Available	
	1x5 g[25]	1% vaginal cream	7-14	Not available	
	1x5 g[25]	2% vaginal cream	3	Not available	
Ekonazol	2x150 mg[1]	150 mg vaginal suppository	1	Not available	C[28]
	1x150 mg1		3		
Mikonazol	1x5 g[25]	2% vaginal cream	7	Not available	C[28]
	1x5 g[25]	4% vaginal cream	3	Not available	
	1x100 mg[25]	100 mg, 200 mg, 1.200 mg	7	Not available	
	1x200 mg[25]	vaginal suppository	3	Not available	
	1x1.200mg[25]		1	Not available	

Note: FDA: *Food and Drug Administration;* IU: *International Unit;* g: gram; mg: milligram
* Health care facility level 1,2, and 3 (Indonesian National Formulary 2021)[31]
** Health care facility level 2 and 3 (Indonesian National Formulary 2021)[31]

During pregnancy, treatment with topical imidazole has been shown to be more effective than treatment with topical nystatin.[1] The cure rate with clotrimazole therapy is higher than with nystatin.[4] Although clotrimazole and nystatin have been used to treat VVC for more than 40 years, both drugs are still effective.[4,30] The goal of VVC treatment is not to eradicate all the fungi in the lower genital tract, but to reduce their number so that the patient is free from clinical symptoms.[1]

In pregnancy, the susceptibility to infectious diseases increases so that it can cause not only mixed vaginitis infections, especially in the last trimester of pregnancy but also cause complicated vaginal dysbiosis so that clinical manifestations become more severe.[32] The prevalence of mixed vaginal infections is 6.5–61.0% during pregnancy and 2.4–10.0% for non-pregnant women.[32] Mixed vaginal infections in late pregnancy can lead to an increased incidence and risk of peripartum infections.[32] In one Indonesian research, the most common cause of vaginal discharge was infection with Candida spp. along with bacterial vaginosis.[26]

In addition, other co-infections in small amounts, namely *Candida* spp. along with *Trichomonas vaginalis, Chlamydia trachomatis,* and *Neisseria gonorrhoeae* were also found.[26] It is necessary to consider the presence of infections other than *Candida* spp. if clinical manifestations of vaginitis are more severe, prolonged or repeated for more comprehensive management.

Probiotic Therapy for Vulvovaginal Candidiasis

Some lactobacilli have antagonistic effects against *Candida,* for example *Lactobacillus rhamnosus.*[1] Administering *L. rhamnosus* twice daily vaginally for one week after the administration of intravaginal miconazole, decreased the recurrence rate of VVC within 6 months after treatment.[1] Decreased *Lactobacillus* is found in vaginitis due to mixed infections.[32] Several investigators demonstrated that vaginal *Lactobacillus* has a major inhibitory effect on *C. albicans* and *C. glabrata.*[18]

This protective effect is mainly due to its ability to attach to vaginal epithelial cells, compete for nutrients, inhibit adhesion of pathogens to receptors on epithelial cells, and inhibit the growth of pathogens.[1] Lactobacilli have been identified as having antifungal or immunostimulatory effects in vitro.[1] It is also known to significantly reduce in vivo fungal colonization after VVC therapy.[1] Another study reported that *L. plantarum* increased the effectiveness of a single dose of 500 mg clotrimazole in preventing recurrence of VVC.[1]

Although probiotic marketing for VVC treatment is increased, further research is needed to prove its benefits.[33] In addition, there is considerable heterogeneity across studies (e.g. route of administration, type of probiotic and duration of use of probiotic).[33] Before recommending the use of probiotics for the treatment of VVC, further quality studies are needed.

CONCLUSION

Pregnancy is a risk factor for increasing Candida spp. colonization in the vulvovagina. Colonization of Candida spp. during pregnancy can be symptomatic or asymptomatic. The diagnosis of the VVC is made based on clinical manifestation and mycological laboratory tests (microscopic examination and/or fungal culture). Intravaginal clotrimazole or nystatin are options in the management of VVC in pregnancy. Do not give any oral antifungal as the management of VVC in pregnancy because of the risk causing congenital abnormalities in the fetus. Therapy for asymptomatic Candida spp. colonization in pregnancy is still debated. The use of probiotics in the management of VVC still requires further research.

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