

Pathogenesis, Diagnosis and Treatment of Vaginitis and Cervicitis in Clinical Practice

¹MurtazaMustafa,²Bendaman B Yanggau,³HelenLasimbang
^{1,2,3}Faculty of Medicine and Health Sciences, University Malaysia Sabah, KotaKinabalu,
Sabah,Malaysia.

ABSTRACT: Vulvovaginitis results with the loss of *Lactobacillus*-dominated normal vaginal flora,with the sexual activity pathogenic organisms are introduced into the vagina. *Lactobacillus* maintain normal vaginal pH of 3.5,and production of hydrogen peroxide which is bactericidal. Primarily vaginitis include three infections,trichomoniasis,vulvovaginalcandidiasis, and bacterial vaginosis(BV),desquamative inflammatory vaginitis(DIV), associated with estrogen deficiency. Cervicitis primarilyendocervicitis caused by sexually transmittedpathogens.Vaginal pathogens include: *Candidaalbicans*, *Trichomonasvaginalis*,*Neisseriagonorrhoeae*,*C.trichomatis*,*Gardnerrelavaginalis*.Drugs of choice for candidiasis, Fluconazole 150mg orally in a single dose with vaginal preparations,and metronidazole for trichomoniasis.Patienthistory,complete examination,and laboratory tests are essential for diagnosis of vaginitis or cervicitis.

KEYWORDS:Vaginitis,Trichomoniasis,Cervicitis,Treatment.

I. INTRODUCTION

Vulvovaginal symptoms are common and frequently result in encounter of patients with healthcaresystem,including use of folk remedies, purchase of over-the counter (OTC) pharmaceuticals,and presentations to healthcare providers [1].Cervicitis may be infectious or noninfectious is primarily an endocervicitis caused by *Neisseria gonorrhoeae*,*C.trachomatis* or both of these sexually transmitted pathogens [2].The normal vaginal secretions are a physiologically important biomass.Vaginal cells contain glycogen and are continually shed into the lumen of vagina.As the cells autolyze,glycogen depolymerizes to glucosewhich serves as energy source for bacteria known as lactobacilli.*Lactobacillus crispatus*and *lactobacilli jensenii*are the predominant species [3].Lactobacilli metabolize glucose to lactic acid,which results in a normal vaginal pH of 3.5 to 4.6.Lactobacilli also produce hydrogen peroxide, which is bactericidal alone and highly bactericidal in combination with physiologic amounts of myeloperoxidase and chloride [4].Loss of the normal *Lactobacillus*-dominated vaginal flora increases the likelihood of exogenous infection after exposure to sexually transmitted pathogens, as well as the risk of endogenous infection in association with pregnancy and gynecologic surgery[5,6].In addition to normal secretions,the differential diagnosis of vaginal discharge primarily includes three infections,e.g.trichomoniasis, vulvovaginal candidiasis and bacterial vaginosis (BV);an idiopathic condition known as desquamative inflammatory vaginitis (DIV);cervicitis, both infectious and noninfectious, andvulvovaginitis associated with estrogen deficiency [7].Patient medical history should include all of the usual gynecologic parameters, including menstrual history, pregnancies,contraception,sexual preference(sexual orientation),past and present sexual relationships, and prior genitourinary infections, underlyingmedical conditions such as allergies,diabetes, malignancies, andimmunodeficiency syndrome (primarily human immunodeficiency virus (HIV) disease) that might be associated with vulvovaginal disease [7].Common pathogens include: *Candida albicans*,*Trichomonasvaginalis*,*Neisseriagonorrhoeae*,*C.trichomatis*,*Gardnerellavaginalis* and others. Treatment of candidiasis, uncomplicated or complicated is different. Effective drugs for candidiasis include Fluconazole150mg orally in a single dose with vaginal preparationsand metronidazole for trichomoniasis.The paper reviews pathogenesis, diagnosis and therapy of vaginitis and cervicitis.

II. CANDIDA VULVOVAGINITIS

Etiologic agent and pathogenesis

Candida albicans can be isolated from about 80% to 90% of patients with vulvovaginal candidiasis,and the other yeasts account for up to 20% of cases [8].*Candida tropicalis* is isolated from about 1% to 5% and may be associated with a higher rate of recurrence after standard treatment [9].*Candida* (formerly *Torulopsis*) *glabrata* accounts for about 10% of vaginal yeast isolates [8].Symptomatic vaginitis caused by this organism is associated with less intense itching and dyspareunia than caused by other *Candida*species, but organism may be

harder to eradicate with standard therapies[10].the relative incidence of vaginitis caused by fungi other than *C.albicans* appears to be increasing. Non-*albicans* infections are associated with recurrent disease (accounting 21% of recurrent vs 12% of initial infections) and with HIV infection (22% of infections in HIV-positive women vs 12% in HIV-negative women), especially in HIV-infected women who receive prophylaxis with imidazoles[9].It is thought that the widespread use of topical antifungal agents, especially short courses ,may contribute to selection for non-*albicans* yeasts, which are less susceptible to these agents than is *C.albicans*.Cases of vaginitis caused by *Saccharomyces cerevisiae* have been reported and may be associated with baking[11].Some workers have estimated that 75%ofadult women will suffer at least one episode of vulvovaginal candidiasis during their life time[12].Inhibition of normal bacterial flora by antibiotics favors the growth of yeasts, althoughsymptomatic cases are seen after the use of antimicrobials that do not suppress lactobacilli.Vulvovaginal candidiasis sometimes occurs after antimicrobial treatment of trichomonas or BV [12].Growth of yeasts is apparently favored by high estrogen levels, although such levels also promote the growth of lactobacilli[13].The prevalence of carriage of *Candida* is higher among users of oral contraceptives than woman using other methods of birth control. The mechanism of this estrogenic predisposition is unclear [14].Vulvovaginal candidiasis is associated with poorly controlled diabetes mellitus, and tight glycemic control decreases the frequency symptomatic infection [15].However, testing for diabetes in women with recurrent vulvovaginal candidiasis is not cost effective [14].It has been suggested that tight insulating clothing predisposes to vulvovaginal candidiasis by increasing vulval warmth and moisture. In prospective studies, a higher prevalence of candida carriage and higher concentrations of organisms were found in women who wore tight rather loose clothing [15].Impairment of phagocytic or of cell-mediated immunity (e.g.transplantation,chemotherapy)alsopredisposes to vulvovaginalcandidiasis.Some authoritiesbelieve that women with HIV infection develop vulvovaginal candidiasis more often than HIV-negative women do, especiallyif they have low CD4 T-cell count[16]

The contribution of sexual transmission is poorly defined.Vovovaginal candidiasis increases in incidence with onset of sexual activity, but incidence is also increased by the use of oral contraceptives, the contraceptive sponge, or the intrauterine device, any of which might coincide with sexual activity[17,14,18]Having multiple sexual partners is not associated with higher incidence of Candida infection.Most women who present with vulvovaginal candidiasis have no predisposing illness or medications [7] The mechanism by which Candidaproduces disease is not well defined. Although it is postulated that differences in virulence must exist, strains isolated from symptomatic women are not demonstrably different from isolates from asymptomatic carriers [14,19] Filamentous forms(hyphae and pseudohyphae) are associated with active disease.Pseudohyphae have been observed to penetrate vaginal epithelial cells, and they are more adherent to cells than are budding yeasts(blast pores)[20-22].Adherence appears to be an important pathogenic feature of *Candida* spp,and sublethal concentrations ofantifungal agents may ameliorate disease by reducing adherence [23,24].The severity of symptoms in vulvovaginal candidiasis is not directly related to the number of yeast cells present. Indeed very small numbers of yeasts may be present in vaginal material recovered from highly symptomatic women [14].An immunologic reaction has been suggested as the mechanism for symptomatic disease in such women, and one small series suggested that desensitization may decrease the frequency of symptomatic episodes[25,26].

III. CLINICAL PRESENTATION

Patients with candida vulvovagnitis generally complain of perivaginalperuritis,often with little or no discharge. Dysuria is occasionally noted and is likely to be perceivedas vulvar rather than urethral.The labia may be pale or erytheomatous.Shallow,radial,linear ulceration, especially in the posterior portion of the introitus,,are common.Excoriations caused by scratching are often present, just beyond the main area helped diagnostically. The vaginal walls may erythematous.Candidal discharge is classically thick and adherent.However, it may be thin and loose, resembling the discharge of other vaginitides[7].

Diagnosis of *Candida* vaginitis : Vaginal pH is usually normal. There is no odor when the vaginal secretion are mixed with 10% KOH(whiff test).Microscopic examination of vaginal material in saline or in 10% KOH may disclose budding yeasts or mycelia. In the symptomatic patient with a diagnostic microscopic examination, fungal cultures are not needed. Microscopic examination of vaginal secretion is incompletely sensitive, however.Accordingly cultures may be helpful to secure the diagnosis in a patient who has a compatible clinical presentation and a negative microscopic examination. It is usually expedient to treat such a patient with antifungal agents while awaiting culture results. Cultures are useful if empirical treatment produces no response [7].

Treatment of *Candida vaginitis*: Therapy of vulvovaginal candidiasis is based on clinical diagnosis e.g. uncomplicated or complicated infection. Uncomplicated vulvovaginal candidiasis is a sporadic infection with *C. albicans*, of mild to moderate severity, in women without a history of recent candidiasis and without underlying illness such as HIV disease or diabetes mellitus. Most patients have uncomplicated disease, and most cases respond to treatment with short courses of vaginal preparations containing nystatin, miconazole, clotrimazole, butconazole, terconazole, and tioconazole. All except nystatin and terconazole containing products are available without prescription [27]. In uncomplicated disease, there does not appear to be any difference in efficiency related to dosage from vaginal tablets, suppositories, ointment, creams or length of treatment (1, 3, 7 or 14 days). Oral fluconazole in a single 150mg dose is as effective as aforementioned vaginal medications [28].

III. TRICHOMONIASIS

Etiologic agent and pathogenesis

Trichomoniasis is caused by the protozoan *Trichomonas vaginalis*. It is classic exogenous sexually transmitted infection, like gonorrhea and chlamydial infection. The organism is not normally present in the vagina. Transmission almost always occurs through sexual contact. After an incubation period of few days, patients develop a purulent discharge associated with varying degrees of vulval irritation, dysuria, and dyspareunia. An abnormal odor is often present usually signifying concomitant BV [7].

Diagnostic tests: Most patients present with vestibular and vaginal erythema and a purulent vaginal discharge. A minority of patients' manifest characteristic mucosal capillary dilation, which gives the mucosa a strawberry appearance [7]. Vaginal pH, is always greater than 4.5. A positive whiff test is not unusual. The vaginal wet preparation contains abundance of leukocytes and motile flagellated. The wet preparation have sensitivity of 60% to 70% in symptomatic patients [29]. Non-culture tests include OSOM Trichomonas Rapid Test (Genzyme), Affirm VOIII (Becton Dickinson), and XenoStrip Tv (Xenotype Diagnostic). These tests have sensitivity that approaches that of culture [30]. Sensitive and specific nucleic acid amplification tests have also been developed [31]. Diagnostic tests in which organisms are no longer motile may lack specificity. A common clinical problem is the women with no epidemiologic evidence for a sexually transmitted condition who has trichomonads visualized on a cervical cytological examination. In some such cases, the cytologist may misread the smear [32].

Treatment of Trichomoniasis : Metronidazole and tinidazole are the only effective agents that are approved by the FDA for the treatment of trichomoniasis. A single 2-g oral dose of metronidazole or tinidazole can be prescribed. Alternatively, 500 mg oral metronidazole be given twice daily for 7 days. Controlled studies have failed to show any important advantage of the 7-day regimen. A single-dose regimen if administered under direct observation in the office or in the clinic has the obvious advantage of 100% compliance. Because the trichomoniasis is almost always sexually transmitted, treatment with metronidazole of recent sexual partners. Regardless of their symptoms, is an integral part of management [33]. For patients who cannot tolerate metronidazole at this dosage level and for those who do not respond to it, tinidazole has better in-vitro efficacy, is better tolerated than metronidazole, and has cured most patients with metronidazole resistant trichomoniasis [34]. *Trichomonas vaginalis* organisms have been shown to be estrogen dependent in vitro and in vivo [35, 36]. In one report, discontinuation of estrogen replacement treatment in a postmenopausal woman was associated with resolution of vaginal trichomoniasis [37]. Human immunodeficiency virus (HIV) infections has no effect on the incidence or prevalence of trichomoniasis or on persistence or recurrence [38]. Metronidazole has traditionally been avoided during pregnancy because of largely theoretical concerns about mutagenicity and oncogenicity. However, studies and meta analyses have not demonstrated a consistent association between metronidazole use during pregnancy and teratogenic or mutagenic effects in infants [39].

IV. BACTERIAL VAGINOSIS

Etiologic agent and pathogenesis

Bacterial vaginosis (BV) was initially described in sexually active women, and it is common in populations with high prevalence of sexually transmitted diseases [40]. BV was first described by Gardner *et al.* for the women who present to their physician with vaginal symptoms have a specific condition [41]. Discharge is often present at the introitus and visible on the labia minora. The labia and vulva are not erythematous or edematous. On speculum examination, the vaginal walls appear uninflamed. The vagina usually contains a grayish, thin homogenous discharge. A pungent odor may be noted by the examiner. The endocervix is unaffected by the process, and any cervical discharge should be physiological. The presence of a purulent cervical discharge may result from coincident gonococcal or chlamydial infection [42]. Abnormalities on

bimanual examination is unusual in uncomplicated BV and should prompt a search for other pathologic process. That is an increased risk of endometritis and salpingitis among women with BV [43]. Microscopic examination of vaginal discharge in BV characteristically reveals flora of coccobacilli, *Gardnerellavaginalis* (formerly *Haemophilusvaginalis*). Although Gardner regularly produced BV by inoculating fresh vaginal discharge from patients with BV into vagina of healthy volunteers, inoculation of pure culture of *G.vaginalis* was far less likely to produce disease [43]. The explanation of all these observations is that *G.vaginalis* is not the single cause of BV. BV is usually a synergistic infection involving not only *G.vaginalis* but also other microorganisms. The total number of organisms dramatically increased in the vaginas of women with BV [44]. Hydrogen peroxide-producing lactobacilli dominate the normal vaginal flora, and appear to protect against exogenous infection. Some workers believe that an undefined change in the vaginal milieu permits the replacement of protective H₂O₂-producing lactobacilli with *G.vaginalis* and other microorganisms [3]. Some investigators have linked douching to BV [45]. Women who have BV are at increased risk for development of infection with herpes simplex virus type 2, *N.gonorrhoeae* and *C.trachomatis* [46,5].

Diagnosis of BV: The patient is most likely to complain of odor and of discharge which tends to be gray and homogenous. The odor is best described a "fishy" is caused by amines such as trimethylamine. These amines volatilize at increased pH, which explains the propensity of the patient to notice the odor when the selections are more (e.g. during menses, after intercourse). Vulvovaginal irritation is not usually prominent symptom hence the use of term vaginosis rather vaginitis [7]. Microscopic examination of vaginal secretions suspended in 0.9% NCL reveals few leukocytes and many small bacilli. These bacilli tend to coat vaginal epithelial—so called "clue cells", name by Herman Gardner because they provided a clue to the diagnosis of this condition [7]. Symptoms of BV include: (a) homogenous vaginal discharge, (b) fishy vaginal odor, (c) during menstruation & after intercourse, (d) minimal itching or irritation [7]. Criteria for the diagnosis of BV include (i) homogenous vaginal discharge, (ii) vaginal pH greater than 4.6, (iii) positive whiff test with 10% KOH, (iv) clue cells. Asmel and colleagues [47], suggested at least three of four listed criteria be present for the diagnosis of BV to be made. Criteria developed by Nugent and colleagues for the diagnosis of BV with use of the Gram stain [48]. Highly sensitive tests such as polymerase chain reaction (PCR) directed at *G.vaginalis* are not useful due to high prevalence of *G.vaginalis* among health individuals [49].

Treatment of BV : The primary regimen for the treatment of BV is oral metronidazole, 500 mg twice a day for 7 days. A single 2.0-g dose of metronidazole such as used to treat trichomoniasis is less effective and is not recommended [50]. Vaginal preparations containing 0.75% metronidazole gel or 2% clindamycin cream or ovules containing 100 mg of clindamycin are effective and have few systemic effects [51-53]. Treatment failure occur fairly commonly, presumably because normal Lactobacillus-dominated flora fails to become established after anaerobes and other components of BV flora have been reduced in number with use of antimicrobial agents [54]. Recent studies has shown that persistence of *G.vaginalis* in biofilms on the vaginal wall may associated with treatment failure [55].

V. CERVICITIS

Etiologic agent and Pathogenesis

Infectious cervicitis is primarily an endocervicitis caused by *N.gonorrhoeae*, *C.trichomatis* or both of these sexually transmitted pathogens [2]. Primary herpes simplex virus infection can cause endocervicitis, but seldom occurs without vulvar lesions that make the diagnosis obvious. *Mycoplasma genitalium* has recently been associated with cervicitis [2]. Noninfectious cervicitis is usually is ectocervicitis in which there is inflammation in an ectropion [7].

Diagnosis and treatment : The patient usually complains of a purulent vaginal discharge. The mucopurulent secretions are not irritating, so there is no vulvar discomfort or introital dyspareunia. Because gonococcal or chlamydial infection can involve the urethra, endometrium, or adnexa, there may be dysuria, abnormal uterine bleeding, lower abdominal pain, or pelvic dyspareunia [7]. Findings on examination of vulva and the vaginal mucosa are usually normal. In infectious endocervicitis, the purulent secretions can be seen to flow from the endocervical canal; in noninfectious cervicitis, the purulent secretions can be seen to emanate from the ectropion [7]. Vaginal pH may be elevated. There is no odor when secretions are mixed with 10% KOH. Wet preparations of vaginal secretions contain many leukocytes. Vaginal cells are mature. Gram-stained smears of cervical secretions confirm the presence of many leukocytes, and in gonococcal infection, may contain intracellular cocci. Culture or non-culture for *N.gonorrhoeae* and *C.trachomatis* should be performed [7]. Patients who have positive tests for sexually transmitted bacteria should be treated with regimens recommended for the etiologic agent. [33] If tests for gonococcal and chlamydia are negative antimicrobial treatment will not likely to be of benefit. If the volume of secretions from an ectropion is bothersome, destruction of the endocervical

mucosa of the ectropion with cryotherapy may allow the endocervix to become reepithelialized with squamous epithelium, with a resultant diminution of the volume of the ectrocervical secretions [7].

VI. DESEQUAMATIVE INFLAMMATORY VAGINITIS

Etiologic agent and pathogenesis

DIV is an unusual condition of unknown cause. It mimics estrogen deficiency vaginitis and trichomoniasis but usually occurs in women of reproductive age who have normal hormonal function and no evidence of any sexually transmitted conditions [7]. This disorder sometimes occurs in premenopausal women or after pregnancy suggesting a role for changes in the level of estrogen in its etiology [56].

Diagnosis and treatment: The main characteristics of DIV include: (a) purulent discharge (b) vulvar discomfort (c) dyspareunia, and findings are mucosal erythema, purulent secretions, and parabasal cells. The vaginal pH often elevated to greater than 4.6. There is no odor when the vaginal secretions are mixed with 10% KOH. The saline preparation contains many leukocytes. Most of the vaginal epithelial cells are immature parabasal cells [56]. The primary regimen for the treatment of DIV is topical corticosteroids and topical boric acid provide systematic relief. Relapse is predictable after these agents are discontinued. By far the most effective treatment for this condition is 2% clindamycin vaginal cream is inserted into the vagina at bedtime for 14 days [56].

VII. ESTROGEN DEFICIENCY VAGINITIS

Etiologic agent and pathogenesis

Estrogen deficiency vaginitis is seen in postmenopausal women and in younger women who have become estrogen deficient because of disease or because of treatment with pharmaceuticals that interfere with the production of estrogen [57]. This condition can also be seen during breastfeeding because of an effect of prolactin on estrogen production. [58]. Without estrogen vaginal mucosa thins. Glycogen is decreased and as a result lactobacilli no longer dominate the vaginal flora. Thinning of the mucosa may result in vulvar discomfort and introital dyspareunia. The thin vaginal mucosa may become infected with enteric organisms and others that are able to colonize the vagina in the absence of lactobacilli [7].

Diagnosis and treatment : Vaginal secretions, if present may be purulent. Vaginal pH is elevated. There is no odor when the secretions are mixed with 10% KOH. Microscopic examination of the secretions discloses immature (parabasal) vaginal cells with or without leukocytes. Vaginal cultures contain a variety of enteric and other bacteria [7]. The treatment involves estrogen replacement or cessation of antiestrogenic drugs or breastfeeding. Topical antibacterial agents containing sulfonamides or clindamycin may improve symptomatic vaginitis and lubrication agents may relieve vaginal dryness and dyspareunia [7].

VIII. CONCLUSION

A complete history, "whiff test", pH measurement of vaginal secretions, and careful evaluation will help the diagnosis and treatment of vaginitis and cervicitis.

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