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Genital discharge in females- A Review

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Abstract

Sexually transmitted infections (STIs) are major public health problem. In pre pubertal age group, gonococcal and chlamydia infections are common. In post pubertal age group, it is due to bacterial vaginosis, trichomoniasis and candidiasis. In post-menopausal age, desquamative inflammatory vaginitis is most common. Sexually transmitted infection/reproductive tract infections (RTIs), in nonpregnant females have tremendous adverse consequences and can lead to pain, organ damage, pelvic inflammatory diseases, infertility, and ectopic pregnancy. Even though, pregnant females are regarded as low-risk group for acquiring infections, the effect and consequences are of more serious nature compared with the nonpregnant counterpart recent studies suggest that a decrease in lactobacilli may increase women's susceptibility to heterosexually acquired human immunodeficiency virus infection. Physicians need to be aware of emerging epidemiological data, the varying clinical presentations of vaginal discharge, and how to approach their management so that the symptom can be treated according to its aetiology. These infections can only be prevented if all patients are counselled and educated properly. Condom use has to be promoted and demonstrated. Partner treatment has to be stressed and notification slip to each partner has to be issued. Apart from all these factors, HIV testing is mandatory in all the cases.

Keywords: Trichomoniasis, Bacterial vaginosis, Desquamative inflammatory vaginitis.

Introduction

The normal anatomy, physiology and microbial ecology of the vagina are age dependent. The type of infections also differs in various age groups. In the neonatal period, maternal estrogen influences the vaginal mucosa. It is lined by stratified squamous epithelium and resists infections. In the pre pubertal age group, vaginal mucosa is lined by cuboidal cells and has a high pH of 7. Following puberty, estrogen secretion causes a change again to stratified squamous epithelium and the presence of lacto bacilli changes the pH to 4.0-4.5. In post-menopausal age, the vaginal epithelium becomes thin and pH increases.[1]

Depending on the various ages, the susceptibility of infections and types of conditions change. In pre pubertal age group because of columnar epithelium, gonococcal and chlamydia infections are common. In post pubertal age group, vaginal discharge is due to three common conditions like bacterial vaginosis, trichomoniasis and candidiasis. In post-menopausal age, desquamative inflammatory vaginitis is most common.[2]

The first definitive study of vaginal flora was published by Doderlein in 1894. The normal flora of the vagina is highly susceptible to the local environment and hormonal influences. After puberty, in response to estrogen secretion, glycogen is deposited in the vaginal epithelium.[3] Glycogen is an optimal substrate for the growth of lactobacilli. Lactobacilli produce lactic acid from glucose, keeping the vagina at an acidic pH. Lactobacilli may produce substrates and enzymes which interact with other organisms in the female genital tract.[4] Recent studies suggest that a decrease in lactobacilli may increase women's susceptibility to heterosexually acquired human immunodeficiency virus infection.[5] *L.crispatus* and *L.jensenii* are the two common species identified in the normal flora. Nearly all women are vaginally colonized by obligatory anaerobic Gram-negative rods and '*peptostreptococcus'* species.[6] Mucus secreted by the goblet epithelial cells in the cervix also plays a role in defense. It basically provides lubrication and selective separation from exogenous macromolecules.[7]

Vaginal discharge is one of the commonest problems encountered in clinical practice. Trichomoniasis, bacterial vaginosis and yeast infections are the three most frequent causes of vaginal discharge.[8] Other causes of vaginal discharge are given in Table 1.

Trichomoniasis: The etiological agent *Trichomonas vaginalis* (TV) was first identified by Donne who visualized motile microorganisms in the purulent frothy vaginal discharge of women who presented with genital irritation and genital discharge.[9]

T.vaginalis is a parasitic protozoan, causes trichomoniasis, which has a worldwide distribution. Annual incidence of this infection is estimated around 170 million worldwide.[10] It amounts for 50% of sexually transmitted infections.[8] The exact incidence in our country is not known but ranges from 1-24%.[11] Humans are the natural host for TV. The disease has an incubation period of 5-28 days.[11] Both sexes may be asymptomatic; the disease also may be self-limiting making the diagnosis more difficult.

Symptoms in females may include vaginal discharge, odor, edema or erythema and strawberry

cervix (colpitis macularis). Dysuria and lower abdominal pain may be other complaints.[9,12] Women infected during pregnancy are predisposed to premature rupture of membranes, premature labor and low birth weight infants.[13] In addition, TV may amplify HIV transmission.[14]

Diagnosis is based on the classical clinical features. However these can be seen only in a few individuals or the symptoms are common to other STDs and strawberry cervix is seen only in 2% or frothy discharge in 10% of patients only. The time honored investigation is demonstration of the parasite in the wet mount collected from vaginal discharge. The organism is identified by its size (10 x 7 µm), its shape and its twitching mobility. For this reason, the specimen has to be immediately processed. Still, this procedure detects only 35-85% of cases depending on the expertise of the microbiologist. Another disadvantage is that there should be a minimum concentration of 10^4 organisms necessary for identification under wet mount.[15]

The broth culture method is the gold standard for the diagnosis of trichomoniasis. Diamond's medium or the in pouch TV culture system can be used for culture. It takes 2-7 days and 300-500 trichomonads/ml of inoculum is necessary for the growth. A number of other staining techniques using acridine orange, Leishman, or per-iodic acid- Schiff and Fontanna have been used to improve the sensitivity of direct microscopy. However, papanicolaou (pap) staining has been insensitive.[16,17]

Metronidazole and tinidazole are effective in the treatment. Current CDC guidelines recommend metronidazole can be administered orally as 2 g single dose or as 500 mg twice a day for 7 days. Tinidazole can be given as 2 g single dose.[18] Oral therapy is preferred because there is concurrent infection of the urethra and periurethral glands. Single dose therapy with 2 gm has shown higher cure rates and is preferred as it ensures compliance. Both these drugs can produce a cure rate of 90-100%. Clinical resistance is considered when there is failure to cure the infection after at least two consecutive courses of metronidazole. Resistance is observed in 2-5% of patients. Resistance is treated with 2 g orally for five days.[19-22]

Candidiasis: The earliest clinical description of candidiasis was given by Wilkinson in the year 1894.[20] Incidence of vulvovaginal candidiasis is incomplete, as it is not a reported entity. This condition affects females at least once in life time. The age of candidiasis corresponds to the peak sexual activitiy i.e., third and fourth decades. Most of the studies were conducted in special clinics like STD clinics, ante natal clinics, etc., and hence a complete picture of incidence is lacking.[23-25] But across the world, it is the second most common cause of vaginal infections.

More than 90% of strains isolated from vaginal smears belong to the species *Candida albicans* and the remainder *Candida glabrata*. Vaginal candidiasis due to non albicans strain is on the rise.[26] Candida organisms gain access to the vaginal lumen from adjacent perianal area.[27] *Candida albicans* is never a commensal in the vagina.

Pregnancy predisposes to Candida infection, as well as oral contraceptives, use of condoms, diabetic women and broad spectrum antibiotics. Symptomatic vaginitis is most common in the third trimester as well as recurrent vaginitis. Estrogen in pregnancy enhances adherence of yeast cells to the vaginal mucosa. Broad spectrum antibiotics remove the protective vaginal bacterial flora. Low numbers of lactobacilli have been found in such patients.[28] Other factors like tight clothing, non-cotton under wear, commercial douches, feminine hygiene sprays also contribute to alteration of vaginal milieu and transfer of asymptomatic to symptomatic vaginitis.[29]

Acute pruritus and vaginal discharge are the usual presenting symptoms, but both are not specific as they share several disorders. Vulvar pruritus is most common in symptomatic patients. Vaginal discharge is frequently minimal, non-odorous, with discrete papulo pustular peripheral lesions. There is adherent curdy white discharge, with erythema of vaginal epithelium and the cervix is essentially normal. Copious vaginal discharge and white plaques are observed in some patients only justifying the term 'vaginal thrush'. At the other end, some patients may have only minimal erythema but which may extend to the perineum and groin.[26]

Diagnosis can be confirmed by wet mount which is helpful to exclude a motile trichomonad or a clue cell. A 10% potassium hydroxide (KOH) preparation is extremely valuable in identifying germinative yeasts, and shows sensitivity rate of 65 to 85%.[30] If there are many white cells it denotes a mixed infection. Estimation of vaginal pH reveals normal in candidiasis whereas in trichomoniasis or bacterial vaginosis it is in excess of 5. Vaginal cultures are performed in patients with high clinical suspicion and negative microscopy. Reliable cultures are obtained using Nickerson's medium or semi quantitative slide-stix cultures. Pap smear is unreliable as a diagnostic modality yielding only 25% results in culture positive patients. A positive culture does not necessarily indicate that the yeast is responsible for the vaginal symptoms. Yeast cell numbers directly correlate with vaginal symptoms. There is no advantage of one media over the other. There are also no serological tests. Latest rapid tests include a latex agglutination technique using polyclonal antibodies.[31] Candidiasis can easily be differentiated from trichomoniasis and bacterial vaginosis. [Table 1]

Table 1: Causes of vaginal discharge

Physiological	Pathological infectious	Pathological non infectious
Sexual arousal	Trichomoniasis	Detergents (Nonoxynol)
Pregnancy	Candidiasis	Foreign body (cervical caps)
Pre menstrual	Bacterial vaginosis	Herbal
	Neisseria gonorrhea *	
	Chlamydia infections*	
	Herpes simplex virus*	

*Infects endocervix, vaginal discharge is secondary.

Treatment includes topical azoles. Azoles are used in various concentrations as creams, ointments and vaginal pessaries.[32,33] Nystatin 1,00,000 units vaginal tablet, one tablet for fourteen days has become the standard therapy during pregnancy. Other azoles like butaconazole 2% cream 5 gm intra vaginally for three days or clotrimazole 1% cream 5 gm intra vaginally for 7-14 days, or clotrimazole 100 mg vaginal tablet for seven days or miconazole 2% cream 5 g intra vaginally for seven days or Tioconazole 6.5% ointment 5 g intra vaginally in a single application have all been recommended. There is no superiority of one over the other agent. Cure rates are of 80-90%. Oral systemic azole agents have shown marginally higher cure rates. Azoles are fungistatic agents, which is a drawback in therapy. Itraconazole 200 mg two doses or fluconazole 150 mg single dose are equivalent to topical therapies but not superior.[34] Management of vulvovaginitis in pregnancy is more difficult, as clinical response is slower and recurrences are common. Longer duration of therapy is needed to eradicate yeast infection.[34,35] All topical agents can be used throughout pregnancy. Oral azoles are contra indicated.[20]

Bacterial vaginosis:[36,37] Bacterial vaginosis (BV) is the most common cause of vaginal symptoms of child bearing age. Doderlein described a non-motile bacillus, which he considered as the normal vaginal flora of pregnant women. Doderlein bacillus later became known as lacto bacilli. *Lactobacillus* was least pathogenic. Vaginal discharge was considered to be a shift in the vaginal flora from predominance of *Lactobacillus* to predominance of anaerobes. *Gardnerella vaginalis* was recognized to be associated with non-specific vaginitis in 1955.[38] The term BV was considered as it is associated with vaginal over growth of not only anaerobic bacteria but also by certain species of facultative bacteria and genital mycoplasma.[39]

A high prevalence of BV has been reported in women attending STD clinics, which ranges from 24-37%. In Thailand BV was reported in 33% of female sex workers in comparison to 16% of women from antenatal clinic.[40] BV is observed commonly in sexually experienced females than in virgins. Similarly, multiple sex partners also showed an increased incidence of BV. Other risk factors include, douching for hygiene, use of intra uterine device and oral contraceptive users.[41]

Over the last three decades it has been proved beyond doubt that *Gardnerella vaginalis* has been associated with BV. However this has also been cultured from vaginal discharge of asymptomatic women.[41] Hence, it has been thought that *G.vaginalis* interacts with anaerobic bacteria and genital mycoplasmas to cause BV. Anaerobic gram-negative rods most commonly associated with BV include *Preovotella, Porphyromonas, Bacteroides, Ureolyticus* and *Fusobacterium nucleatum.* Another anaerobic gram-negative rod, *Mobiluncus* was also associated with BV. Among the genital mycoplasmas, *M.hominis* was associated with 63% of women with BV whereas only in 10% of normal controls. All these proved that BV results from the replacement of the normal vaginal flora (*Lactobacillus*) with a mixed flora consisting of *Gardnerella vaginalis*, anerobes and *M.hominis*. Thus most studies of the pathogenesis of BV have focused on how the microbial eco system of the vagina has been altered. *Lactobacillus* species normally resists vaginal and cervical infection. Further, it was also pointed out that women with H_2O_2 producing lactobacilli, gives more protection, as H_2O_2 is more toxic to organisms causing BV.

Amines produced by the microbial flora, perhaps microbial decarboxylases, account for the characteristic abnormal fishy odor produced by the vaginal fluid if mixed with 10% KOH. This is called as "Whiff test" which is due to volatilization of aromatic amines at alkaline pH. This test is positive in 43% of patients. *Mobiluncus* is known to produce trimethylamine, which is responsible for the odor.

The most common symptom of BV is malodor, observed in 49% of patients. Vaginal discharge is non-viscous, homogenous, white, uniformly adherent, noticed in 69%. Vaginal pH is approximately 4.5 when measured with a pH paper.

Amsel's criteria for diagnosis are:[42]

1. A homogenous, white, non-inflammatory discharge that smoothly coats the vaginal walls
2. Vaginal pH >4.5
3. Positive Whiff test i.e., typical fishy odor on addition of one drop of 10% KOH to vaginal discharge
4. Few or no lactobacilli
5. Presence of 20% clue cells in vaginal discharge

BV during pregnancy is associated with adverse pregnancy outcomes. These women are at risk of pre-term delivery.

Lab diagnosis of bacterial vaginosis is by demonstration of clue cells.[43] These are vaginal squamous epithelial cells coated with anaerobic gram

variable coccobacilli, *Gardernella vaginalis* which adheres to exfoliated vaginal epithelial cells and this creates a shaggy looking clue cells which are characteristic. Clue cells can be demonstrated by microscopic examination of vaginal wet mount preparation. Bacterial amines together with organic or acetic and succnic acids are cytotoxic which leads to exfoliation of epithelial cells. The normal vaginal squamous epithelial cells have distinct cell margins and lack granularity. Clue cells are seen as squamous cells with a large number of coccobacillary organisms densely attached in clusters to their surfaces giving them a granular appearance. The edges of squamous cells show instead of sharp borders, indistinct or stippled borders. Presence of more than 20% clue cells in vaginal discharge is included in Amsel's criteria for the diagnosis of BV. Polymorphs can be demonstrated in the normal vaginal wet mount preparation. In BV there is lack of polymorphs. A rapid card test has been developed for detection of trimethylamine combined with elevated pH in the vaginal fluid. Nugent proposed a scoring system for BV. A score of 7 is diagnostic, 4-6 is indeterminate and <3 is negative.

Table 2: Differentiating features of common vaginal discharge

Features	Normal	Trichomoniasis	Candidiasis	Bacterial vaginosis
Microbiology	*Lactobacilli L. jensenii L. crispatus*	*T. vaginalis*	*C. vaginalis C. glabrata*	*Gardenerella M. hominus Mobiluncus spp Bacteroids spp Prevotella*
Symptoms	None	Purulent discharge	Vulval itching and irritation	Malodorous discharge
Discharge amount	Scant/none	Profuse	Scanty	Moderate
Color	Clear	Yellow	White	Gray/milky
Consistency	Non homogenous	Frothy	Curdy, adherent	Homogenous non adherent
Vaginal epitheliu m	Normal	Erythematous	Erythematous	No inflammation
pH	<4.5	5.0	>4.5	>4.5
Whiff test	--	May be +	--	++
Microscopy	Normal epithelial cells and lactobacilli	Leukocytes and trichomonads	Ovoid budding yeasts	Clue cells

Treatment of BV is with metronidazole which has produced 87% cure with doses of 500 mgs twice a day for 7 days. Single oral dose of 2 g produced less cure rates than 7 days therapy. To decrease systemic side effects of oral agents intra vaginal therapies has been evaluated. Intra vaginal tablets of 500mg per day for seven days showed cure rates of 76%. Similarly, oral clindamycin with 300 mg twice a day for 7 days was clinically effective in 94% of patients. Oral clindamycin was also effective in pregnant women. Intra vaginal clindamycin have also been studied using various strengths and it was found that 2%, one full applicator (5g) intra vaginally at bed time for seven days was most effective. Oral metronidazole is not teratogenic in humans. However, some prefer the intra vaginal route for lack of side effects. Follow-up is done after one month of treatment. Alternative regimens are used to treat recurrent disease. Low risk pregnant women should be treated with metronidazole 250 mg three times a day for seven days.[19,20]

All three common conditions can be differentiated. The features are discussed in Table 2.

Desquamative inflammatory vaginitis: Desquamative inflammatory vaginitis (DIV) was described in 1968.[44] It is defined by its clinical and wet mount characteristics and is a diagnosis of exclusion. DIV presents with dyspareunia, burning and vaginal discharge. Clinically and microscopically, the discharge is purulent in nature. Clinicians unfamiliar with this condition may misdiagnose this with various other dermatoses like bacterial vaginosis, candidiasis and treat the same. On clinical examination, vulva shows introital redness and extension of erythema to labia minora. In more marked cases, the vagina can be covered with small red macules, reminiscent of strawberry cervix of trichomoniasis. There are no erosions in vagina.[45] Abnormal vaginal discharge is present, abundant and yellowish in color, with a pH greater than 5. Green and grey secretions also have been found.

A wet mount shows an increase in white blood cells and parabasal cells. These are immature squamous epithelial cells shed from a vaginal epithelium that is rapidly proliferating because of inflammation. Lactobacilli are absent as the pH is greater than 5. A culture may yield *Streptococcus agalactiae* but treatment with antibiotics will not improve the situation.[46]

Criteria for diagnosis are:[46]

1. Clinically purulent vaginal discharge
2. Variable redness of the vaginal mucosa
3. pH >5
4. Wet mount showing increase in leukocytes and parabasal cells
5. Absence of lactobacilli
6. Negative bacterial cultures

Biopsies showed non-specific lichenoid infiltrate.[45] Treatment is with topical 2% clindamycin cream intra vaginally for two to four weeks, but, it is not known if this improvement is due to bacterial etiology. Clindamycin has non-specific anti-inflammatory and antibacterial properties. Topical corticosteroid also helps in some patients. Hence, DIV is considered as hypersensitivity or autoimmune phenomenon.[47,48]

Cytolytic vaginosis:[49] Cytolytic vaginosis (CV) should be suspected in patients who have signs and symptoms of vaginal candidiasis, which is unresponsive to anti-fungal drugs. This condition is known to be lactobacillus overgrowth syndrome or Doderlein's cytolysis. Lactobacillus results in lysis of vaginal epithelial cells and therefore called as cytolytic vaginosis. Lactobacilli in low numbers up to five per ten squamous cells in vaginal discharges are considered as protective against vaginal candidiasis. Overgrowth of lactobacilli may cause damage to vaginal epithelium. This dissolution causes symptoms like dysuria, pruritus and dyspareunia. The symptoms are more pronounced in the luteal phase. The diagnostic criteria include:[50]

1. High risk suspicion
2. Absence *of Trichomonas, Gardnerella or candida* on wet smear
3. An increase in number of lactobacilli
4. Paucity of white blood cells
5. Evidence of cytolysis
6. Presence of discharge
7. pH between 3.5-4.5

Treatment is directed towards reducing the number of lactobacilli by increasing the pH. This involves douching with sodium bicarbonate solution or using a sodium bicarbonate suppository vaginally. Douches are carried out twice a day, for two weeks.[51]

Cervical infections

Genital chlamydial infection: *Chlamydia trachomatis* is the commonest bacterial sexually transmitted disease worldwide.[52] Half of 90 million cases encountered annually belong to south east Asia.[53] The order *Chlamydias* comprised one family, *Chlamydiaceae* and one genus *Chlamydia*, containing three species. D to k serotype is associated with variety of genital tract diseases.[54] The cervix would seem to be the primary target of infection but vaginal infections are noticed even in patients after hysterectomy. Infection of the cervix with *C.trachomatis* is often asymptomatic. These patients may develop symptoms in three months time. Mucopurulent discharge is found in 37% of women and hypertrophic ectopy in 19%. Hypertrophic ectopy means edematous, congested and bleeds easily.[53] The number of PMN leukocytes in cervical mucus is correlated with cervical infection with *Chlamydia.* Gram stained smears show >30 PMN leukocytes per 1000 field of cervical mucus. Clinical diagnosis of chlamydial cervicitis depends on a high degree of suspicion and careful clinical examination. There are no genital symptoms correlated with chlamydial infection.

Being an intra-cellular pathogen, *C.trachomatis* requires a cell culture system for propagation in the laboratory, which is the gold standard for diagnosis. Nearly all women with endocervical infection develop antibodies to *C.trachomatis* in serum as assessed by the micro –IF assay. The most exciting recent development in chlamydial diagnostic testing has been PCR or LCR from cervical, urethral or urinary specimens from males and females. These tests show a specificity of > 99%.[54]

The most active drugs against *C.trachomatis* in tissue culture are rifampicin, tetracyclines, macrolides, sulfonamides, fluoroquinolones and clindamycin. There are no reports of antimicrobial resistance.[20]

Gonococcal infections: In adults, only mucous membranes lined by columnar or cuboidal, non-cornified epithelial cells are susceptible to gonococcal infection. Progressive mucosal damage and sub mucosal invasion are accompanied by a vigorous polymorphonuclear leukocyte response, sub mucosal micro abscess formation and exudation of purulent material into the lumen of infected organ. The endo cervical canal is the primary site of urogenital infection in women.[55] Urethral colonization is present in 70-90% of infected women. After hysterectomy urethra is the primary site of infection. Increased vaginal discharge, dysuria, inter menstrual uterine bleeding and menorrhagia may all occur alone or in combination in varying severity. Purulent exudates may be expressed from urethra, periurethral glands or the Bartholin's gland duct. Complications in pregnancy include spontaneous abortion and pre mature rupture of membranes, pre mature delivery and ophthalmia neonatorum.

Isolation of *N.gonorrhoeae* is the diagnostic standard for gonococcal infection. Modified Thayer-Martin medium has been the gold standard for many decades. Microscopic examination of clinical material using Gram's stain has also been studied and the simplest. Gram negative diplococcic with typical morphology are identified within or closely associated with PMNL. Serological tests have been developed to detect antibodies *to N.gonorrhoeae* like complement fixation, immunoprecipitation, immunofluorescence, hemeagglutination, latex agglutination and ELISA.[55,56]

For over a decade, ceftriaxone, a third generation cephalosporin has been used as single intra muscular injection in a dose of 125 mg. Cefixime, an orally absorbed cephalosporin, provides a useful alternative was also recommended since 1993. Epidemiologic treatment includes treatment of all partners exposed within two weeks prior to the onset of symptoms or to the diagnosis of index case.[20]

Syndromic approach: WHO recommends that patients who present for primary care with symptoms that suggest sexually transmitted infections (STI) in settings where resources are scarce be treated syndromically using algorithms or clinical flow charts. In many countries, syndromic STI care is now a principal national HIV/ STI prevention control strategy. The objectives of syndromic STI management are to provide rapid relief of symptoms, to treat all infections effectively, to avoid harm and unnecessary treatment and to prevent future STIs in individual patients and communities.

Unfortunately, not all STI related syndromes are equally amenable to syndromic management strategies. For example, genital discharge syndrome in women is particularly difficult to treat through the use of algorithms. Most studies revealed that algorithms for urethral discharge in men and genital ulcer disease in both men and women are highly sensitive. But, the algorithm for vaginal discharge is not highly sensitive. There is an urgent need for the development of affordable, rapid and effective diagnostic technique that will improve STD detection in resource poor setting.[58]

Conclusion

Vaginal discharge is the most common syndrome encountered in clinical practice. These infections can only be prevented if all patients are counseled and educated properly. Condom use has to be promoted and demonstrated. Partner treatment has to be stressed and notification slip to each partner has to be issued. Apart from all these factors, HIV testing has to be done in all cases.

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