

Managing Vulvar Infections: HPV-Related Disease and Candidiasis

Pathogenesis, risk factors, diagnosis, and treatment

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Infections of the vulva can be broadly divided into two general categories: those associated with sexually transmitted diseases and those of nonvenereal etiology. Some of these infections, such as vulvar schistosomiasis or leishmaniasis, are rarely encountered in general medical practice in the United States.

This article is the second of a two-part series on infections of the vulva. The first article (which appeared in the November 2000 issue of *Women's Health in Primary Care*) focused on herpes simplex virus. This article will focus on human papillomavirus (HPV) and *Candida*—two common causes of vulvar infections that are at times difficult to diagnose and treat effectively. Epidemiology, symptomatology, diagnostic evaluation, and treatment are reviewed.

HUMAN PAPILLOMAVIRUS

Although more than 20 million reproductive-age women and men have evidence of anogenital HPV infection, the clinical manifestations of such infection (eg, external genital warts, neoplasm of the cervix or

ABSTRACT: Vulvar infections, whether sexually transmitted or nonvenereal, are commonly seen in primary care practice. Anogenital human papillomavirus infection can be found in more than 20 million reproductive-age women and men, although less than 5% show clinical manifestations. Treatment options include patient-applied creams, provider-applied acids, and, in severe cases, surgery. Of all the causes of nonvenereal vulvovaginal infections, perhaps the most common culprit is *Candida*. About 40% to 75% of sexually active women have experienced the symptoms of vulvovaginal candidiasis: itching, irritation, soreness, pain with intercourse, burning on urination, and a white, curdlike discharge. The nature of the infection will dictate treatment, which may include topical and oral therapy. (*Women Health Primary Care* 2000; 3(12):857-862)

vulva) occur in less than 5% of those affected. Infection with HPV is, therefore, widespread yet rarely symptomatic.¹ In a cohort of nearly 5,000 young women (ages 13 to 22) screened for HPV, 20% tested positive for the infection, but less than 5% of the total cohort had evidence of severe cervical dysplasia.² Furthermore, during the 20- to 30-month

observation period, 60% to 75% of the infected cohort under study became HPV-negative.² Infection with HPV, then, appears to be transient for most patients.

Although transmission of anogenital HPV infection occurs largely via sexual intercourse, fomite-associated transmission has been reported. Peak infection levels are found in women who are in their late teens and early 20s. Other risk factors for infection include an increased number of sexual partners, an increased number of partners of the woman's male partners, a long sexual relationship, and immunosuppression.³

Of the more than 100 HPV subtypes presently identified, approximately 35 are specific to the anogenital tract. Current probes for HPV testing allow for the identification of half of these anogenital subtypes, including five low-risk and 13 high-risk, or oncogenic, subtypes. Whether such testing should be added to cytologic screening is currently under consideration, but at present the routine use of HPV testing in the diagnosis of vulvar manifestations is not recommended. In

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general, HPV low-risk subtypes 6 and (less commonly) 11 are implicated in the development of genital warts.⁴ The oncogenic subtypes 16 and 18 are found in many precancerous vulvar intraepithelial neoplasias, as well as in squamous cell cancers of the vulva.⁵

CLINICAL FINDINGS

When clinical manifestations of HPV infection do occur, they often present as bumps or growths on the vulvovaginal or perianal mucosa. Although these growths are almost always asymptomatic, they can cause itching, burning, pain, or bleeding. On examination, condyloma can range in morphologic appearance from flat-topped papules to flesh-colored, dome-shaped papules to keratotic warts. Actual condyloma acuminatum appears as irregular growths that resemble small heads of cauliflower. Condylomata

allow accurate diagnosis and appropriate therapy.

In general, lesions that appear hyperpigmented, indurated, fixed, or ulcerative, or that do not respond to the modalities listed below, should be biopsied using a standard punch biopsy under local anesthesia. Erythema alone does not warrant biopsy unless it is persistent and unexplained. When a woman presents with vulvar erythema as her only symptom, a careful check for other causes, such as vulvovaginal candidiasis and contact dermatitis, should be performed before biopsy is considered.

Women with vulvar condylomata should undergo routine cervical screening with Papanicolaou smears. If cervical warts are found during examination or if vulvar neoplasia is confirmed by biopsy, referral for colposcopic evaluation is indicated.⁶ For women with re-

ment (eg, following organ transplantation), as well as immunosuppressed women infected with the human immunodeficiency virus (HIV). Treatment of such patients is often frustrating, as recurrences are frequent.⁸

PREGNANCY AND HPV INFECTION

Women with HPV infection who are pregnant or who are considering pregnancy pose specific challenges. In addition to the potential for rapid proliferation of external genital warts during pregnancy, the mere presence of HPV infection raises concerns regarding how the baby will be delivered and its risk of contracting oropharyngeal or genital HPV infections. Treatment of pregnant women with genital warts can be accomplished by one or more of the modalities discussed below—with some notable exceptions.

The only contraindication to vaginal delivery is obstruction of the birth canal by extensive condylomata.⁹ Although neonates are at greater risk of exposure to HPV following vaginal delivery than they are after cesarean section,^{10,11} the significance of such exposure remains controversial. Moreover, cesarean section does not offer absolute protection.¹² At present, the data regarding long-term sequelae in infants and children infected with HPV at delivery are inconsistent and do not justify routine cesarean section in women with genital warts.¹³

TREATMENT

Condylomata treatment includes a variety of pharmacologic (Table 1) and surgical options. Clinical trials suggest similar clearance rates, ranging from roughly 30% to higher than 80%, for the widely accepted treatment modalities listed below.

Patient-applied therapies: Imiquimod 5% cream and podofilox 0.5% solution and gel are available

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acuminata tend to occur on the moist surfaces of the vulva, introitus, and perianal area. Keratotic and smooth papular types occur more often on fully keratinized skin. Flat warts can occur on either type of skin surface.³

DIAGNOSIS

Distinguishing genital warts from vulvar neoplasia on the basis of appearance alone is not always possible. Although most biopsied lesions demonstrate condyloma, a small subset shows other vulvar skin disorders, neoplasia, or even cancer. Identifying patients who require biopsy is critical, as it will

current perianal warts and a history of anoreceptive intercourse, anoscopy is warranted.³

REGRESSION AND RECURRENCE

Spontaneous regression of genital condylomata occurs in up to 28% of affected patients.⁷ In contrast, certain physical and medical conditions allow for proliferation of external genital warts and, in some instances, vulvar neoplasias or cancers. Women who are at increased risk of developing warts and neoplasias include those receiving long-term corticosteroid therapy (eg, for asthma or lupus) or chronic immunosuppressive treat-

for patient application. Imiquimod, applied to the wart, is used three times weekly for up to 16 weeks. Podofilox is used twice daily for three days followed by four days without therapy; the cycle may be repeated up to four times.

Provider-applied therapies:

These treatments include podophyllin resin 10% to 25% in a compound tincture of benzoin, and trichloroacetic or bichloroacetic acid 80% to 90%. Podophyllin resin should be carefully applied to the wart and then washed off by the patient one to four hours after application. When using trichloroacetic or bichloroacetic acid, first coat the surrounding normal epithelium with a protective substance (eg, 2% lidocaine jelly or baking soda), and then use a small cotton-tipped applicator to carefully apply the medication to the wart. On contact with the acid, the skin will turn white.

Local irritation (including pain, burning, and soreness), erythema, edema, and, at times, ulceration can result from the use of any of these medications. Careless or excessive use can cause extensive burning of the epithelium, with resultant scar formation.¹⁴

Other options: Most patients will present with a small number of genital warts that should respond to any one of the previously described pharmacologic therapies. However, other outpatient treatment options include cryotherapy, with repeated applications weekly or biweekly, and excision or curettage under local anesthesia. Surgical excision or laser vaporization of genital warts is usually reserved for patients with high volumes of condylomata, and such patients should most likely be referred to a specialist for treatment. Treatment with intralesional interferon and 5-fluorouracil/epinephrine gel implants, although effective, has been limited because of side effects and expense.³

Table 1. Treatment for condyloma

Therapy	Treatment	Application
Patient-applied	Imiquimod 5% cream	Three times weekly for up to 16 weeks
	Podofilox 0.5% solution and gel	Twice daily for three days followed by four days without therapy; the cycle may be repeated up to four times
Provider-applied	Podophyllin resin 10% to 25% in compound tincture of benzoin	Carefully applied to the wart and then washed off by the patient between one and four hours after application
	Trichloroacetic or bichloroacetic acid 80% to 90%	First, the surrounding normal epithelium is coated with a protective substance, eg, 2% lidocaine jelly or baking soda, and then a small cotton-tipped applicator is used to carefully apply the medication to the wart

In the subset of patients who do not respond to one of the above therapies, further evaluation is needed to establish a diagnosis because multiple other vulvar skin disorders, in addition to vulvar neoplasia, can mimic genital warts. For example, the lesions of secondary syphilis (condylomata lata) or squamous cell hyperplasia can be difficult to distinguish from genital warts and require, respectively, further serologic testing or a biopsy of a representative area.

Treatment during pregnancy:

In the ambulatory setting, appropriate treatment choices for pregnant women include trichloroacetic or bichloroacetic acid and ablative procedures, such as cryosurgery. For small or single lesions, excision under local anesthesia is also an option. Rarely, patients will require larger excisions and/or laser vaporization, either of which can be done in the operating room.

Podofilox and podophyllin are recognized teratogens, and pregnant woman should not be exposed to them. Although imiquimod is listed under category B, its use during pregnancy is also not recommended.⁶

CAVEAT

A nonhealing vulvar ulceration, an area of unexplained hyperpigmen-

tation, or any suspicious vulvar growth or skin change should be evaluated in a timely fashion with punch biopsy or the patient should be referred to an appropriate specialist.

CANDIDA

Of all the causes of nonvenereal vulvovaginal infections, perhaps the most common culprit is *Candida*. The majority of candidal infections are sporadic and, in 85% to 90% of cases, caused by *Candida albicans*. The non-*albicans* species (the most common of which are *Candida glabrata* and, to a lesser extent, *Candida parapsilosis* and *Candida tropicalis*) should be suspected in cases of resistant candidiasis.¹⁵ Although reported rates of infection vary, an estimated 40% to 75% of sexually active women have experienced the symptoms associated with vulvovaginal candidiasis: itching, irritation, soreness, pain with intercourse, burning on urination, and a white, curdlike discharge.^{16,17}

RISK FACTORS

Candidal infections are rare before the onset of menarche. They peak in the third to fourth decade of life and occur more often in women who have poorly controlled diabetes, who are severely immuno-

suppressed, or who are pregnant. Behavioral factors associated with the development of this infection are varied. Purported risk factors include the frequency of recent sexual activity (one study showed a fourfold increase of candidal infections among women who had had intercourse seven or more times weekly¹⁶) and oral-genital con-

tact.¹⁸ Antibiotics, including tetracycline, ampicillin, the cephalosporins, and topical metronidazole or clindamycin, as well as topical iodine solutions, have also been implicated, yet most women using antibiotics do not develop yeast infections.^{15,19} Vaginal colonization by *Candida* organisms may therefore be required before symptoms

will develop in a woman taking antibiotics.

Various contraceptives, including the vaginal sponge, diaphragm, condom, and intrauterine device, increase the risk of infection.^{20,21} The role of oral contraceptives is uncertain. Although some studies indicate that they increase the risk of infection, other evidence shows that the low-dose second- and third-generation pills add no risk.²² In an extensive study of more than 1,000 college students, Foxman¹⁶ found no difference in the risk of candidal infections between non-users of birth control and users of oral contraceptives, diaphragms, condoms, and spermicides.

Table 2. Treatment for candidal infections of the vulva

	Treatment	Application
Standard regimens	Topical agents	
	Miconazole	2% cream, 1 applicator/d for 7 days
		100-mg suppository/d for 7 days
		200-mg suppository/d for 3 days
		1200-mg suppository single dose
	Clotrimazole	1% cream, 1 applicator/d for 7 – 14 days
		100-mg vaginal tablet/d for 7 days
		200-mg vaginal tablet/d for 3 days
		500-mg vaginal tablet in single application
	Butoconazole	2% cream, 1 applicator/d for 3 days
	Terconazole	0.4% cream, 1 applicator/d for 7 days
		0.8% cream, 1 applicator/d for 3 days
		80-mg vaginal suppository/d for 3 days
	Nystatin	100,000 U vaginal tablet/d for 14 days
	Tioconazole	6.5% ointment, 1 intravaginal applicator dose
2% cream, 5 g/d for 3 days		
Oral agents		
Fluconazole	150 mg PO as single dose	
Ketoconazole	200 mg/d PO for 5 days	
Itraconazole	200 mg PO bid for one day	
	200 mg/d PO for 3 days	
Recurrent infections	Topical agents	
	Azole agents	Any of the topical azole agents listed above can be used as extended therapy for 14 – 21 days
	Boric acid	600-mg capsule intravaginally bid for 14 days
	Oral agents	
	Fluconazole	100 – 200 mg PO for single dose with concomitant vaginal therapy
Itraconazole	100 – 200 mg/d PO for 3 days	
Ketoconazole	400 mg/d (2 tablets) PO for 5 – 14 days	
Suppressive	Oral agents	
	Clotrimazole	500 mg PO once weekly for 6 months
	Fluconazole	100 mg PO weekly for 6 months
	Ketoconazole	100 mg PO weekly for 6 months

DIAGNOSIS

A reliable diagnosis cannot be based on symptoms (none of which are highly sensitive or specific) or the results of a physical examination; corroborative laboratory data are necessary. For example, in a study by Ferris et al,²³ only 35% of women previously diagnosed with vulvovaginal candidiasis were able to correctly diagnose the classic symptoms of such an infection. Moreover, these women were more likely to inappropriately use over-the-counter antifungal medications to treat a variety of other potentially serious infections (eg, pelvic inflammatory disease, bacterial vaginosis, and urinary tract infections).²³

Direct microscopy—including the estimation of vaginal pH (which remains normal at 4.0 to 4.5) and the finding of blastospores, hyphae, or pseudohyphae in saline and 10% potassium hydroxide preparations—is necessary to establish the diagnosis. Estimation of vaginal pH has a sensitivity of 30% to 50% for vulvovaginal candidiasis; the sensitivity of finding blastospores, hyphae, or pseudohyphae is slightly higher (65% to 85%).^{15,19}

Vaginal cultures are indicated in symptomatic women, with or without corroborative physical

findings, when microscopy results are negative. Reserving culture for this population will result in treatment being given to 90% of the women who fulfill the criteria for vulvovaginal candidiasis; it will also limit the use of culture to those women in whom the rate of positive cultures will be greater than the background prevalence of *C albicans* in asymptomatic women without signs of infection (33% versus 10%).²⁴

TREATMENT

The nature of the infection will dictate treatment choices (Table 2).

Uncomplicated fungal infections may be treated by either topical or oral therapy. Because topical therapy may initially cause irritation, oral treatment may be preferable. Of the oral therapies, both fluconazole and itraconazole have good safety profiles and are well tolerated, and they lack the risk of complications, primarily hepatotoxicity, posed by ketoconazole. (Note, however, that itraconazole is not approved by the Food and Drug Administration for vaginal yeast treatment.)

Women with a history of repeated infections require extended therapy with either topical or oral treatment. Extended topical therapy is also indicated for pregnant women who were not cured by single-application, high-dose topical therapy. Oral therapy is contraindicated during pregnancy.¹⁵ Severe vulvitis is more effectively treated with seven-day topical azole therapy than with single-dose fluconazole, although combination therapy with a low-potency topical corticosteroid may be required to alleviate the symptoms of severe infection.¹⁹

True recurrent vulvovaginal candidiasis (defined as four or more proven infections per year) presents more of a challenge in both evaluation and treatment. Although testing for diabetes or immunosuppression is often suggest-

ed, in only a minority of patients will such testing be profitable. Women with recurrent candidiasis who have risk factors for HIV infection should undergo testing for HIV.¹⁵ Although non-*albicans* species should be suspected and culture is clearly warranted in

women with recurrent disease, it should be remembered that repeated vulvovaginitis does occur with persistent *C albicans*. Lastly, although some advocate the testing and treatment of the male partners of women with recurrent candidiasis,²⁵ such practice has met

PRIMARY POINTS

Infections of the Vulva

Infection with human papillomavirus is widespread, yet it is rarely symptomatic. Infections peak in women who are in their late teens and early twenties. Other risk factors include increased number of sexual partners, increased number of partners of the woman's male partners, duration of the sexual relationship, and immunosuppression.

Condyloma can range in morphologic appearance from flat-topped papules to flesh-colored, dome-shaped papules to keratotic warts. Actual condyloma acuminatum appears as irregular growths that resemble small heads of cauliflower.

Women with vulvar condylomata should undergo routine cervical screening with Papanicolaou smears. If cervical warts are found during examination or if vulvar neoplasia is confirmed by biopsy, referral for colposcopic evaluation is indicated.

Vulvovaginal candidiasis is one of the most common types of nonvenereal vulvovaginal infections and is caused in nearly 90% of cases by *Candida albicans*.

The diagnosis of *Candida* can be made only by direct microscopy—either through the estimation of vaginal pH (which remains normal at 4.0 to 4.5) or by the finding of blastospores, hyphae, or pseudohyphae in saline and 10% potassium hydroxide preparations.

Although uncomplicated fungal infections may be treated by either topical or oral therapy, oral treatment may be preferable because topical therapy may initially cause irritation. True recurrent vulvovaginal candidiasis is treated with extended regimens followed by at least six months of maintenance therapy.

with varied success,²⁶ and it is not recommended.¹⁹

True recurrent vulvovaginal candidiasis is treated with extended regimens followed by at least six months of maintenance therapy. Without maintenance therapy, 50% of patients will experience clinical relapse within three months. Once maintenance therapy is discontinued, symptomatic relapse rates again approach 50%. As an alternative to long-term maintenance therapy, use of hyposensitization with *Candida* antigen preparation should be considered, as results have been encouraging.¹⁵

Resistant infections are common, particularly in the presence of the non-*albicans* species. For example, approximately half of the strains of *C glabrata* manifest reduced sensitivity to all available azoles. Intravaginal boric acid suppositories have been shown to be highly effective in the treatment of such infections. After a 10- to 14-day course of therapy, cultures should be checked and, when negative, therapy may be discontinued. If the patient's history suggests recurrent disease, maintenance therapy may be initiated (every other day and then twice per week), although little evidence supports such practice.

Another alternative to boric acid is flucytosine cream.¹⁵ Although not available commercially, it can be prepared by a compounding pharmacy (fourteen 500-mg flucytosine capsules ground into 45 g of hydrophilic cream base; the patient should use one 6.4-g vaginal applicator [containing 1,000 mg of active drug] per day for 7 days).²⁷ The expense and potential for the development of resistance limit the use of flucytosine.

Treatment during pregnancy: Pregnant women with candidal infections can be treated with any of the topical azole therapies. Extended therapy (one to two weeks), however, is usually required. Clin-

ical response is often slower, and recurrences are more frequent. Use of the oral azoles, boric acid suppositories, or flucytosine is contraindicated in pregnancy.¹⁵ ❧

REFERENCES

1. Koutsky L. Epidemiology of genital human papillomavirus infection. *Am J Med.* 1997;102:3-8.
2. Moscicki AB, Shiboski S, Broering J, et al. The natural history of human papillomavirus infection as measured by repeated DNA testing in adolescent and young women. *J Pediatr.* 1998;132:277-284.
3. Kiviat N, Koutsky LA, Paavonen J. Cervical neoplasia and other STD-related genital tract neoplasias. In: Holmes KK, Sparling PF, Mardh P-A, et al, eds. *Sexually Transmitted Diseases.* 3rd ed. New York, NY: McGraw-Hill, Health Professions Division; 1999:811-832.
4. Langenberg A, Cone RW, McDougall J, et al. Dual infection with human papillomavirus in a population with overt genital condylomas. *J Am Acad Dermatol.* 1993;28:434-442.
5. IARC Working Group: Studies of Cancer in Humans. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans.* Vol. 64. Lyon, France: International Agency for Research on Cancer; 1995:142-163.
6. Centers for Disease Control and Prevention. 1998 guidelines for treatment of sexually transmitted diseases. *MMWR Morb Mortal Wkly Rep.* 1998;47(RR-1):1-111.
7. The Condylomata International Collaborative Study Group. A comparison of interferon alfa-2a and podophyllin in the treatment of primary condylomata acuminata. *Genitourin Med.* 1991;67:394-399.
8. Drake LA, Ceilley RI, Cornelison RL, et al. Guidelines of care for warts: human papillomavirus. Committee on Guidelines of Care. *J Am Acad Dermatol.* 1995;32:98-103.
9. Wilkinson E. *Genital Human Papillomavirus Infections.* Washington, DC: American College of Obstetricians and Gynecologists Technical Bulletin 193. May 1994:454-460.
10. Tseng CJ, Liang CC, Soong YK, Pao CC. Perinatal transmission of human papillomavirus in infants: relationship between infection rate and mode of delivery. *Obstet Gynecol.* 1998;91:92-96.
11. Tenti P, Zappatore R, Migliora P, et al. Perinatal transmission of human papillomavirus from gravidas with latent infections. *Obstet Gynecol.* 1999;93:475-479.
12. Shah K, Kashima H, Polk BF, et al. Rarity of cesarean delivery in cases of juvenile-onset respiratory papillomatosis.

13. Watts DH, Brunham RC. Sexually transmitted diseases including HIV infection in pregnancy. In: Holmes KK, Sparling PF, Mardh P-A, et al, eds. *Sexually Transmitted Diseases.* 3rd ed. New York, NY: McGraw-Hill, Health Professions Division; 1999:1089-1132.
14. Higgins SP, Stedman YF, Chandiock P. Severe genital ulceration in two females following self-treatment with podophyllin solutions [letter]. *Genitourin Med.* 1994;70:146-147.
15. Sobel JD. Vulvovaginal candidiasis. In: Holmes KK, Sparling PF, Mardh P-A, et al, eds. *Sexually Transmitted Diseases.* 3rd ed. New York, NY: McGraw-Hill, Health Professions Division; 1999:629-640.
16. Foxman B. The epidemiology of vulvovaginal candidiasis: risk factors. *Am J Public Health.* 1990;80:329-331.
17. Hurley R, De Louvois J. Candida vaginitis. *Postgrad Med J.* 1979;55:645-647.
18. Markos AR, Wade AA, Walzman M. Oral sex and recurrent vulvo-vaginal candidiasis [letter]. *Genitourin Med.* 1992;68:61-62.
19. Sobel JD, Faro S, Force RW, et al. Vulvovaginal candidiasis: epidemiologic, diagnostic, and therapeutic considerations. *Am J Obstet Gynecol.* 1998;178:203-211.
20. Parewijck W, Claeys G, Thiery M, van Kets H. Candidiasis in women fitted with an intrauterine contraceptive device. *Br J Obstet Gynaecol.* 1988;95:408-410.
21. Peddie BA, Bishop V, Bailey RR, McGill H. Relationship between contraceptive method and vaginal flora. *Aust N Z J Obstet Gynaecol.* 1984;24:217-218.
22. Barbone F, Austin H, Louv WC, Alexander WJ. A follow-up study of methods of contraception, sexual activity, and rates of trichomoniasis, candidiasis, and bacterial vaginosis. *Am J Obstet Gynecol.* 1990;163:510-514.
23. Ferris DG, Dekle C, Litaker MS. Women's use of over-the-counter antifungal medications for gynecologic symptoms. *J Fam Pract.* 1996;42:595-600.
24. Eckert LO, Hawes SE, Stevens CE, et al. Vulvovaginal candidiasis: clinical manifestations, risk factors, management algorithm. *Obstet Gynecol.* 1998;92:757-765.
25. Horowitz BJ, Edelstein SW, Lippman L. Sexual transmission of *Candida*. *Obstet Gynecol.* 1987;69:883-886.
26. Spinillo A, Carratta L, Pizzoli G, et al. Recurrent vaginal candidiasis. Results of a cohort study of sexual transmission and intestinal reservoir. *J Reprod Med.* 1992;37:343-347.
27. Horowitz BJ. Topical flucytosine therapy for chronic recurrent *Candida tropicalis* infections. *J Reprod Med.* 1986;31:821-824.