Wolters Kluwer

Treatment of vulvar and vaginal warts

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INTRODUCTION — Vulvar and vaginal warts are one of the clinical manifestations of human papillomavirus (HPV) infection (picture 1A-C). Approximately 90 percent of anogenital warts are associated with HPV types 6 and/or 11, which are of low oncogenic potential [1-3]. Additional HPV types (including high oncogenic risk types) may be identified, but usually as co-infections with HPV 6 or 11.

For most patients, the presence of genital warts is concerning because of their cosmetic appearance, association with a sexually transmitted disease, bothersome symptoms, absence of a cure, and social stigma [4]. Although treatment can eradicate the warts, disease recurrence is common and occurs in 20 to 30 percent of patients overall.

This topic will discuss treatment of vulvar and vaginal warts in women. The epidemiology, pathophysiology, clinical manifestations, and diagnosis of anogenital warts, and issues related to men with anogenital infection, are reviewed separately. (See "Condylomata acuminata (anogenital warts) in adults: Epidemiology, pathogenesis, clinical features, and diagnosis" and "Condylomata acuminata (anogenital warts): Management of external condylomata acuminata in men".)

PRETREATMENT COUNSELING — Patients should be given an explanation of their disease and information about the indications for treatment, treatment options, and prognosis. Written material is available from several sources (see 'Information for patients' below).

Information about human papillomavirus infection — Most women want to know how and when they acquired the disease. We tell them that genital human papillomavirus (HPV) is spread by direct physical contact during sex. They may have acquired the infection years prior to diagnosis since the incubation period can last for months and their first recognition of a lesion may represent a relapse rather than a first episode. Therefore, a new diagnosis of genital warts does not mean that the patient or her partner is having sex outside the relationship. We also inform them that condoms provide some protection against HPV transmission, but contact with genital lesions not covered by the condom can result in infection [5].

Patients are also informed that HPV is so widespread that most men and women will have acquired an HPV infection during their lifetime, but are unaware of the infection because it is usually asymptomatic. Acquiring immunity to one type of HPV does not secure immunity against other types, so reinfection can occur. (See "Human papillomavirus infections: Epidemiology and disease associations".)

Indications for treatment — The main indication for treatment of vulvovaginal warts is alleviation of bothersome symptoms (pruritus, bleeding, burning, tenderness, vaginal discharge, pain, obstruction of the vagina, dyspareunia) or psychologic distress [4,6]. Warts do not pose serious risks to health or fertility; therefore, some symptomatic patients may reasonably choose expectant management to see if the warts

spontaneously resolve. In placebo controlled treatment trials, spontaneous regression occurred in up to 40 percent of cases; the remainder remained stable or increased in size or number.

There is no medical indication for treatment of asymptomatic warts incidentally noted on physical examination, but patients should be made aware of the presence of these lesions. There is no reason to believe that treating vulvovaginal warts will reduce a woman's future risk of cancer. Similarly, treatment should not be undertaken to protect sexual contacts since there is no evidence that eradication of warts eliminates infectivity [6,7].

Overview of treatment and prognosis — Patients should be informed that prolonged treatment with frequent follow-up is often necessary. They should also understand that medical and surgical therapies lead to clearance of warts in 35 to 100 percent of patients in 3 to 16 weeks [8], but do not necessarily eradicate all HPV infected cells [6,9,10]. Because clinically and histologically latent HPV can exist beyond the treatment area, the possibility of clinical recurrence or transmission of HPV to sexual partners remains [8]. The likelihood of recurrence is variable depending on the patient's medical condition, immune status, and the extent of disease, but 20 to 30 percent of patients have a recurrence (new lesions at previously treated or new sites) within a few months [11]. Nevertheless, most HPV infections associated with genital warts in immune competent patients are cleared within two years [12].

Both medical and surgical options are available for treatment. Treatment effectiveness studies show highly variable results, possibly reflecting variations in duration of follow-up, drug dosing, criteria for success, severity of disease, patient population, and HPV types. There is no high quality evidence that any treatment is significantly superior to another or appropriate for all patients and all types of warts; therefore, treatment choice is based on the location, number, and size of the warts; patient characteristics (eg, pregnancy, ability to comply with therapy, immunocompromise); availability of resources and clinical expertise; and patient preferences after considering side effects, cost, and convenience (table 1) [13-27]. Medical therapies are generally tried first; if the patient has not responded to the initial medical therapy after 3 weeks or complete clearance has not occurred by 6 to 12 weeks, a different medical therapy can be administered [28]. Surgical therapy is typically reserved for patients with extensive and/or bulky lesions and those who have failed to respond adequately to medical therapy. Surgery results in high initial clearance rates (90 to 100 percent), but recurrence rates are similar to those with medical therapy [8].

Side effects and complications of treatment — All therapies are associated with localized discomfort including itching, burning, erosions, and pain since the epithelium is disrupted [8]. Complications resulting from treatment include hypo- or hyperpigmentation, scarring, and chronic vulvar pain [6]. Hypopigmentation is most common in areas where warts were surgically ablated, but has also been described after treatment with imiquimod. Scarring is most common after surgical procedures that destroy subdermal tissue.

Management of sex partners — Sex partners can benefit from informational counseling. (See 'Information about human papillomavirus infection' above.)

Symptomatic male partners can be referred to their health care provider for evaluation and possible treatment. (See "Condylomata acuminata (anogenital warts): Management of external condylomata acuminata in men".)

Given the high prevalence of infection in adults, high frequency of asymptomatic disease, and absence of curative therapy, testing asymptomatic sexual partners for HPV is not recommended [6]. Screening for other sexually transmitted infections is performed according to standard guidelines. (See "Screening for sexually transmitted infections".)

PRETREATMENT EVALUATION — Determining the human papillomavirus (HPV) type of the warts is unnecessary as this information does not affect clinical management.

The presence of genital warts alone is not an indication for screening for additional sexually transmitted diseases, but such screening is indicated in high risk groups such as women with new partners or in non-

monogamous relationships, and women ≤25 years of age. (See "Screening for sexually transmitted infections".)

Indications for pretreatment biopsy — Biopsy to rule out underlying intraepithelial neoplasia or cancer is not mandatory before initiating therapy, but is recommended when:

- The diagnosis is uncertain. (See "Condylomata acuminata (anogenital warts) in adults: Epidemiology, pathogenesis, clinical features, and diagnosis", section on 'Diagnosis' and "Condylomata acuminata (anogenital warts) in adults: Epidemiology, pathogenesis, clinical features, and diagnosis", section on 'Biopsy'.)
- The lesion has any suspicious features, such as fixation (infiltration of dermis), irregular and unusual pigmentation (red, blue, black, brown), induration, bleeding, ulceration, sudden recent growth, flat.
- The patient is postmenopausal or immunocompromised. (See 'Postmenopausal women' below and 'HIV infected and immunocompromised women' below.)
- The lesion is refractory to medical therapy. (See 'Refractory disease' below.)

The biopsy should be obtained from the most abnormal area and include the edge of the base of the lesion and adjacent tissue. (See "Vulvar lesions: Diagnostic evaluation", section on 'Use of biopsy'.)

TREATMENT OPTIONS

Medical therapy — There are two broad categories of medical therapy: those that directly destroy the wart tissue (cyto-destructive therapies) and those that work through the patient's immune system to clear the wart (immune-mediated therapies). Some of these methods can only be applied in the physician's office, while others can be self-administered by the patient at home [29]. All medical therapies are most useful for patients with limited disease (eg, ≤5 small warts [28]). Some key points regarding medical therapy:

- Podophyllotoxin (podofilox), imiquimod, sinecatechins, and topical interferon can be self-administered.
- Any of the medical therapies discussed below can be used to treat vulvar warts, but vaginal warts can only be treated with trichloroacetic acid (TCA), bichloroacetic acid (BCA), and interferons.
- TCA has no systemic absorption and no known fetal effects; therefore, it is the preferred treatment for pregnant women.
- In general, if the patient has not responded to the initial therapy after about 3 weeks or complete clearance has not occurred by 6 to 12 weeks, it is appropriate to switch to a different treatment [28].

Cytodestructive therapies

Podophyllotoxin (podofilox) and podophyllum resin (podophyllin) — Both drugs are avoided in pregnancy.

- **Podophyllotoxin (**podofilox**)** — Podophyllotoxin (podofilox) contains the biologically active compound from podophyllum resin. Using a cotton swab, the patient applies a 0.5 percent gel or solution to external genital warts twice daily for three consecutive days [6,30]. No more than 0.5 mL of podofilox should be applied in one day. She then withholds treatment for four days, and repeats this cycle weekly up to four times. Large areas (10 cm^2 or more) should not be treated in a single application because pain is likely when the area becomes necrotic.
- Podophyllum **resin** — Podophyllum resin is a plant-based resin that blocks cell division at metaphase and leads to cell death. The clinician applies a 25 percent solution directly to the warts with a cotton swab (or similar device). No more than 0.5 mL should be applied during each treatment session and

large areas (10 cm^2 or more) should not be treated in a single application because of potential pain when the area becomes necrotic. The area should air-dry before the patient dresses.

In contrast to podophyllotoxin, systemic absorption and toxicity have been documented. A weaker solution (10 percent) should be used when treating large warts to minimize total systemic absorption, and application to open lesions/wounds should be avoided.

We instruct the patient to wash the area one to four hours after application of the drug, otherwise excessive skin irritation and systemic absorption can occur. The treatment is repeated weekly for four to six weeks, or until the lesions have cleared. Adverse effects range from mild skin irritation to ulceration and pain, depending upon the concentration used and the length of time it is left on the skin.

Trichloroacetic acid and bichloroacetic acid — Both TCA and BCA are caustic acids that destroy the wart tissue via chemical coagulation of tissue proteins. TCA is used most commonly, and must be applied by a health care provider. It can be used on the vulva and vagina, and during pregnancy.

An 80 to 90 percent TCA solution is applied sparingly to the wart tissue with a cotton swab; the wart turns white as the solution dries. Application of an ointment or gel (such as petroleum or lidocaine jelly) to the normal tissue surrounding the wart can help prevent spreading of acid to unaffected areas. Excessive application of 80 to 90 percent TCA can cause extensive chemical burns of the vagina, vulva and adjacent healthy tissue. If excess TCA is applied, it can be neutralized by washing with soap or sodium bicarbonate solution.

The patient should not sit, stand or dress until the treatment area has dried.

Repeated weekly application is required for four to six weeks, or until the lesions have cleared. The only trial that evaluated use of TCA in women reported a 70 percent clearance rate [31]. Large, thick lesions may not respond because the acid may not penetrate the entire lesion.

Fluorouracil — Fluorouracil (FU) is a pyrimidine antimetabolite that interferes with DNA synthesis by blocking methylation of deoxyuridylic acid, leading to cell death. In the United States, the Food and Drug Administration (FDA) has not approved any formulation of FU for treatment of anogenital warts and its use is contraindicated in pregnancy. A disadvantage of topical FU is that it is often poorly tolerated because of burning, pain, inflammation, edema, or painful ulcerations. For these reasons, topical FU has a limited role in the primary therapy of vulvar or vaginal warts.

A gel consisting of FU and epinephrine in a purified bovine collagen matrix is under investigation. The gel is injected intradermally directly under the wart to create a wheal encompassing it and 5 mm of surrounding tissue. This provides a high concentration of drug for an extended period of time. Injections are performed once per week for up to six weeks. Clearance rates of 65 percent after a median of four treatments have been reported, but 40 percent of patients with a complete response had a recurrence at 90 days follow-up [32]. Side effects include local pain, erosion, ulceration, and urethro-vulvo-vaginitis.

Alternatively, a thin layer of 1 or 5 percent cream has been applied to vulvar or vaginal lesions to cause a chemical desquamation [33-38]. Several dosing protocols have been suggested, ranging from twice daily application to once weekly for several weeks. Zinc oxide cream or petroleum jelly can be applied to unaffected areas as a barrier to help protect against ulceration.

Immune-mediated therapies — Both imiquimod and interferon initiate a local immune response at the site of the wart that ultimately may clear the lesions. Imiquimod and topical interferon may be self-administered; injectable interferon is given in the office. Experience with these agents is more limited than for other medical therapies.

Imiquimod — Imiquimod is a toll-like receptor 7 agonist, which acts as a positive immune response modifier, and stimulates local cytokine induction. Topical treatment of warts increases local production of interferon and reduces human papillomavirus (HPV) virus load [39]. Two formulations are available, Aldara (5

percent imiquimod) and Zyclara (3.75 percent imiquimod), for treatment of external genital warts, but the manufacturers recommend against vaginal administration. There is insufficient information regarding the safety of imiquimod in pregnancy; animal studies suggest this therapy is low risk but use of imiquimod in pregnancy should be avoided until more data are available [6].

The choice between the two formulations should be made based on patient preference, cost and convenience. There are no comparative data available between the two dosing regimens.

Hand washing before and after cream application is recommended. The patient applies imiquimod cream directly to the clean dry warty tissue at bedtime, rubbing it in until the cream is no longer visible; this area is washed with mild soap and water 6 to 10 hours later. Sexual contact should be avoided while the cream is on the skin. The cream can weaken condoms and diaphragms.

Aldara is applied three days per week (eg, Monday-Wednesday-Friday) for up to 16 weeks [6,40-43]. Zyclara is applied daily for up to 8 weeks. A mild, local inflammatory reaction (erythema, induration, ulceration/erosion, itching, burning, vesicles) should occur, which is a sign the drug is working. It is generally not so severe as to preclude further treatment. If severe inflammation occurs, use of the drug should be stopped until the inflammation clears and then it can be restarted at a lower frequency.

Forty to 50 percent of women will have complete clearance of the warts and most of the remainder will have partial clearance, but up to 30 percent will experience a recurrence within 12 weeks. A tube of Aldara 5 percent or Zyclara 3.75 percent costs in the range of USD $800 to $900, but generic formulations are available.

Sinecatechins — Sinecatechins (eg, Veregen) is a botanical drug product for self-administered topical treatment of external anogenital warts. The active ingredient is kunecatechins, which are a mixture of catechins and other components of green tea. The exact mechanism of action of catechins is unknown, but they have both antioxidant and immune enhancing activity. A detailed review of the antiviral, antioxidant, and immunostimulatory properties of green tea catechins is available elsewhere [44].

A 0.5 cm strand of ointment is placed on each wart and a finger is used to cover the wart with a thin layer of the ointment 3 times each day for up to 16 weeks. It should not be used in the vagina or anus and should be washed off of the skin before sexual contact or before inserting a tampon into the vagina. It can weaken the latex in condoms and diaphragms.

Sinecatechins should be avoided in immunocompromised women and women with active genital herpes lesions because safety and efficacy have not been established. There is minimal information on the risk of use during pregnancy. Of note, Veregen costs about $257 for one 15 gram tube.

In two randomized phase III clinical trials, 15 or 10 percent Veregen ointment or placebo was applied to anogenital warts in men and women three times daily until complete clearance of all warts or for up to 16 weeks [45-48]. Veregen was more effective than placebo in achieving complete clearance (54 to 57 versus 34 to 35 percent). Fewer than 10 percent of subjects developed new or recurrent warts [47]. Five percent of subjects discontinued the drug due to side effects and almost 90 percent reported local application site reactions, some of which were severe (pruritus, erythema, pain, inflammation, ulceration, edema, burning, induration, vesicular rash).

Interferons — Interferons have antiviral, antiproliferative, and immune-stimulating effects, theoretically making them an ideal agent for treatment of anogenital warts. Interferon-alpha and -beta have been administered as a systemic therapy (intramuscular injection), topically, and as a subcutaneous intralesional injection. Placebo controlled randomized trials have generally found intralesional therapy to be most effective [49-51], while evidence for the efficacy of systemic and topical therapy has been inconsistent [52-57].

Intralesional injection of 0.5 to 1.5 milli-international units is administered two to three times per week for up to nine weeks. Local anesthesia is recommended [7]. Patients receiving interferons by any route commonly

experience flu-like symptoms, fatigue, anorexia, and local pain [49,55,57].

Given the frequency of bothersome side effects, variable rates of effectiveness, and inconvenience of administration, we don't use interferon for primary treatment of anogenital warts. Interferon may be used as adjunctive therapy to surgical and cyto-destructive treatments, especially in patients with refractory lesions.

Interferons are contraindicated in pregnancy.

Bacillus Calmette-Guerin — Another approach beginning to appear in the literature involves topical administration of bacillus Calmette-Guerin (BCG) [58-60]. It has been used primarily for treatment of perianal warts in men and requires further study.

HPV vaccine — HPV vaccines are effective in the primary prevention of HPV infection. Their use for treatment of anogenital warts or prevention of recurrent disease is investigational and is not recommended at this time. (See "Human papillomavirus vaccination".)

Surgical therapy — Surgical management options consist of ablative and excisional procedures. Not infrequently, and especially in patients with extensive or multifocal disease, both ablative and excisional modalities are used. The choice of method should depend most on the availability of equipment and the surgeon's experience and personal preference. Regardless of the method chosen, the surgeon should maintain control of the depth of tissue destruction since deep destruction of vaginal lesions theoretically could lead to fistula formation.

An advantage of surgical management is that fewer visits for treatment are needed compared with medical therapy, although repeated procedures are sometimes necessary, especially with cryotherapy. A disadvantage of ablative therapies is that persistent hypo- or hyperpigmentation is not uncommon. A disadvantage of all surgical therapies (ablative or excisional) is that they generally require anesthesia and often need to be performed in an operating room; however, small lesions can be ablated or excised in the office with only sedation and local infiltration (eg, lidocaine 1 percent with or without epinephrine) in some highly motivated patients. Lastly, surgical therapy may result in scarring, especially when the subdermal layer is destroyed.

Biopsy is recommended to rule out underlying intraepithelial neoplasia or cancer prior to surgical treatment of lesions that are refractory to medical therapy. (See 'Indications for pretreatment biopsy' above.)

All of the surgical options can be used in pregnant women and on both the vulva and vagina.

Cryoablation — Cryoablation with either liquid nitrogen or nitrous oxide destroys wart tissue via cell lysis. Although it is an office procedure, cryoablation causes pain during application and variable localized inflammation afterward. Providing local anesthesia for the procedure is especially important when the area undergoing cryotherapy is extensive.

Liquid nitrogen is most commonly used, and is applied directly to the vulvar or vaginal lesion with a cotton swab or a fine spray. The treatment is applied for 30 to 60 seconds, until an ice ball forms and encompasses the lesion and 1 to 2 mm surrounding area [61]. Repeated weekly application is required until the lesions have resolved.

Nitrous oxide is dispensed via a cryoprobe and generally gives a greater depth of freezing; therefore, it is not recommended for use in the vagina because of the risk of vaginal perforation and fistula formation [6].

Side effects/adverse reactions include skin irritation, edema, blistering, and ulceration. Post-treatment hypopigmentation is also relatively common.

Laser ablation — Lasers produce light energy, which is absorbed by water within warty tissues, leading to thermal damage and resultant ablation. Carbon dioxide laser is the most commonly utilized type of laser for treatment of vulvar warts, but requires specific training and specialized equipment [26].

Laser ablation is the preferred therapy for extensive or multifocal lesions. In such cases, surgical excision is undesirable since large areas of vulvar skin would have to be removed. Laser is also useful for treating cervical and vaginal warts when surgical excision is technically challenging or not feasible.

A major benefit of using laser rather than the surgical knife on the vulva is that the laser better maintains normal vulvar anatomy. However, up to 28 percent of patients develop some scar formation post-laser surgery [62]. Other risks of laser surgery include pain and hypopigmentation. Rarely, patients may develop chronic pain and vulvodynia [63,64]; patients should be counseled about these risks prior to treatment.

Anogenital warts are epithelial in location; therefore, vaporization should only be carried down to the level of the superficial (papillary) dermis, and no deeper. Scar formation can occur when the laser beam penetrates too deeply. In order to best identify tissue planes and achieve the appropriate depth of treatment, we suggest colposcopic guidance be utilized during the laser procedure [65]. For patients with multifocal or refractory disease, a combination of techniques is often effective. As an example, excision is used to "debulk" the warty tissue, followed by laser ablation of the base (see 'Recurrent disease' below).

The surgeon and operating room personnel should wear protective masks when performing laser ablation, as HPV DNA can be dispersed in the laser plume [66].

Following laser treatment, pain management and careful attention to vulvar hygiene are crucial. Patients are instructed to take sitz baths two to three times a day during the initial one to two weeks following the procedure. Antibacterial creams or ointments are suggested to prevent superficial infection, as well as to separate the vulvar folds and prevent agglutination of tissues. For prevention of agglutination, the patient is instructed to gently separate the vulvar folds each day during healing.

Electrocautery — Electrocautery can also be used for ablation of vulvar or vaginal lesions. An advantage of this approach over cryoablation is that a single treatment session is usually adequate for eliminating the warts. A disadvantage is that electrocautery requires administration of anesthesia and use of an operating room. If available, laser ablation is generally preferable to electrocautery because it is associated with less bleeding and discomfort following the procedure.

Ultrasonic aspiration — The CUSA technique (Cavitron ultrasonic aspirator-CUSA) utilizes ultrasound to fragment and aspirate warty tissue [67]. This allows removal of epithelium without damage to underlying tissue. As with other ablative techniques, exclusion of intraepithelial neoplasia and malignancy is critical prior to treatment by CUSA, since the pathologic specimen obtained is shallow and fragmented and thus may be insufficient to exclude invasion.

Excision — If tissue is needed for histological diagnosis, an excisional biopsy can be performed before an ablative procedure, or an excisional procedure can be performed.

Typically, exophytic lesions are tangentially excised or shaved to the level of normal skin using scissors or a surgical knife, and then the base of the lesion is cauterized [23]. For larger lesions, wide local excision is often required. Adverse sequelae of excisional therapy include pain, dyspareunia, scar formation, and infection [61].

Curettage or electrosurgery can also be used for excision of lesions.

SELECTION OF TREATMENT BASED ON CLINICAL SETTING

Nonpregnant immunocompetent women — In general, if the patient has not responded to the initial therapy after about 3 weeks or complete clearance has not occurred by 6 to 12 weeks, it is appropriate to switch to a different treatment [28].

Limited vulvar disease — The choice of treatment is guided, in part, by insurance coverage, the patient's out-of-pocket costs, and patient preference.

Self-administered therapy — We suggest imiquimod or podophyllotoxin (podofilox) for initial therapy of women with a small area of external genital warts (eg, ≤5 small warts [28]), as long as the patient can comply with home therapy. We prefer imiquimod because of its immune stimulation and demonstrated effectiveness against dysplasia (in case there is any unrecognized dysplasia in the lesion), but its higher cost is a disadvantage. (See 'Imiquimod' above.)

Podophyllotoxin (podofilox) has negligible systemic absorption/toxicity, can be self-administered, and is more effective than podophyllum resin (podophyllin) [68,69]. In a randomized trial comparing podophyllotoxin (podofilox) to podophyllum resin for treatment of warts in women, podophyllotoxin (podofilox) resulted in a higher clearance rate, 71 versus 48 percent [69]. Another comparative trial that included both men and women with genital warts also reported podophyllotoxin was more effective than podophyllum resin for clearance of all warts (84 versus 62 percent of patients had clearance of lesions) [68]. (See 'Podophyllotoxin (podofilox) and podophyllum resin (podophyllin)' above.)

Sinecatechins are a reasonable alternative, but the most costly approach. (See 'Sinecatechins' above.)

If the patient has not responded to monotherapy after about 3 weeks or complete clearance has not occurred by 6 to 12 weeks, it is appropriate to switch to a different monotherapy or cryotherapy. (See 'Cryoablation' above.)

Office based therapy — We suggest trichloroacetic acid (TCA) or cryotherapy for initial office-based treatment of women who cannot comply with self-administered therapy or as a second-line approach for those who fail home therapy [8,70]. (See 'Trichloroacetic acid and bichloroacetic acid' above.) Because of the side effects associated with cryoablation, we prefer medical therapy. (See 'Cryoablation' above.)

For patients who fail monotherapy or cryotherapy, we suggest using TCA in combination with imiquimod [70].

Limited vaginal disease — We suggest TCA for treatment of a small area of vaginal warts (eg, ≤5 small warts [28]). TCA, bichloroacetic acid (BCA), and interferons are the only medications that can be used to treat vaginal warts, but many patients cannot tolerate intralesional interferons. Laser ablation is our preferred surgical approach as it is possible to reach into the vagina and the depth of treatment can be controlled. (See 'Trichloroacetic acid and bichloroacetic acid' above and 'Interferons' above.)

Extensive and/or bulky lesions — For patients with extensive (>20 cm^2) and/or bulky disease, we suggest surgery as initial therapy because medical therapy alone often requires a prolonged course of treatment and is often inadequate and poorly tolerated. Laser ablation is less destructive and less technically challenging than excision, and better tolerated than electrocautery. (See 'Laser ablation' above.)

Recurrent disease — For patients with recurrent disease, the same treatment that resulted in initial clearance of warts may be used again and is likely to be successful.

Refractory disease — For refractory disease, we suggest a surgical approach or a combination of intralesional interferon and TCA. (See 'Interferons' above.) An excisional procedure or biopsy should be performed to exclude intraepithelial neoplasia or cancer by histopathological examination. (See 'Indications for pretreatment biopsy' above.)

A number of trials have examined various combinations of cyto-destructive therapies, immune-mediated therapies, and surgical therapies to minimize recurrence rates, or improve cure rates. Theoretically, the immune-mediated therapies may help reduce the viral load, while the cyto-destructive and surgical therapies can debulk and eradicate the wart tissue. However, results of these trials have been discordant [21,65,71-76].

Postmenopausal women — Postmenopausal women who present with warty-appearing lesions should be biopsied before initiation of therapy, as these women have a greater chance of having an underlying vulvar intraepithelial neoplasia or vulvar cancer than younger women. (See "Vulvar intraepithelial neoplasia" and "Vulvar cancer: Epidemiology, diagnosis, histopathology, and treatment of rare histologies".)

Pregnant women — Three important issues arise when anogenital warts are encountered in pregnancy:

- Worsening of the disease in the pregnant state
- Choice of safe and effective treatment
- Potential vertical transmission to the fetus

There are multiple anecdotal reports of rapid worsening of anogenital warts in pregnant women; however, no studies have compared occurrence and course of clinical warts in pregnant and nonpregnant patients. Pregnancy is associated with a decrease in cell mediated immunity, which may lead to a worsening of viral infection. Few studies have evaluated human papillomavirus (HPV) in pregnancy and most showed an increase in prevalence [77-79].

Indications for treatment of anogenital warts in pregnant women are similar to those for nonpregnant women. In addition, lesions that potentially obstruct the birth canal (vagina and perineum) should be treated to avoid complications during vaginal birth. Treatment may not reduce the risk of vertical transmission (see 'Vertical transmission and mode of delivery' below).

Treatment options are limited in pregnancy because podophyllin, podophyllotoxin, interferon, and FU are all contraindicated because of potential fetal harm. In one case series, four pregnant women with anogenital warts were treated with topical imiquimod 5% cream three times per week for four weeks with no adverse fetal or neonatal effects and significant clearance of lesions (70 percent in two women and 84 percent in the other two women) [80]. However, given the scarcity of data on use of imiquimod or sinecatechins in pregnancy, these drugs are generally not recommended [6].

TCA has no systemic absorption and no known fetal effects; therefore, it is the preferred medical treatment for pregnant women. Clearance rates are highest and recurrence rates lowest when TCA is used in the second half of the pregnancy [81].

Cryoablation is also considered a safe and effective treatment for use in pregnancy [82,83]. We prefer to begin with TCA treatment because it has fewer side effects than cryoablation. (See 'Cryoablation' above.)

A number of case series have described use of laser ablation in pregnancy for bulky, potentially obstructive lesions, with success rates of 90 to 100 percent [84-87]. The risk of wart recurrence appears lowest when the treatment is delayed until the third trimester [84,87]. Isolated, but noteworthy, adverse events reported when laser therapy was used in pregnancy include preterm contractions [85] and preterm delivery [85,86], but a causal association has not been proven.

Vertical transmission and mode of delivery — HPV can manifest in young children as mucosal, conjunctival, or laryngeal disease. Juvenile-onset respiratory papillomatosis (JRP) is the most severe outcome, although rare. Children are usually diagnosed with this condition at 2 to 5 years of age, and may require multiple surgical procedures during their lifetime. (See "Common causes of hoarseness in children", section on 'Papillomatosis (HPV)'.)

Epidemiologic studies have linked JRP to a history of maternal anogenital warts. Early case series reviewed medical histories for mothers of JRP-affected children, and found a history of anogenital warts in about 50 percent of these women [88-91] and a 1 in 400 risk of JRP in infants of mothers with genital warts at delivery [92]. These studies are limited by availability of complete medical information, possible recall bias, and lack of control groups. A subsequent retrospective cohort study overcame some of these limitations with the use of detailed national Danish registries and appropriate selection of a control group [93]. This study reported the rate of JRP was significantly higher in women with a diagnosis of anogenital warts in pregnancy than in nondiagnosed controls, with an estimated rate of transmission of 7 per 1000 affected women. Furthermore, JRP lesions were most likely to carry HPV types 6 and 11, which are the types commonly found in anogenital warts [81]. This association raises important questions as to whether antenatal therapy or elective cesarean delivery can reduce the incidence of this disease in children.

No studies have examined the effect of antenatal treatment of warts on viral transmission to the fetus. Given that treatment of visible lesions is unlikely to eradicate the HPV virus, particularly virus in the upper vagina and endocervical canal, the potential for transmission likely remains even after treatment [94]. Use of the quadrivalent HPV vaccine has been proposed as a means to boost maternal and fetal immunity and decrease vertical transmission rates [95]. However, there are no data to support this theoretical benefit. Given that the vaccine has not been approved or studied in pregnant women, we do not advise this practice.

Early information suggested that neonatal inoculation occurred during passage through the birth canal. DNA analysis of newborn nasopharyngeal aspirates showed a 36 percent detection rate in vaginally delivered infants, with no detection in those delivered by cesarean delivery. However, this study was limited by very low numbers [96]. A separate study looked at cesarean delivery rates for births that were later affected by JRP, and found that the actual cesarean delivery rate was much lower than the expected rate [97]. While these studies suggest that cesarean delivery may protect against neonatal infection, other data limit this conclusion. Neonatal infection has been described following cesarean delivery with unruptured membranes [97,98], and the detection of HPV DNA in placental tissue and cord blood, regardless of mode of delivery, suggests that vertical transmission may occur antepartum [99]. Furthermore, one large retrospective cohort study found no protective benefit of cesarean delivery on the rate of neonatal JRP infection [93].

In view of these data, as well as the potential morbidity of cesarean delivery, and the fact that elective cesarean delivery has not been proven to prevent transmission of HPV, we suggest not performing cesarean delivery for women with anogenital warts for the sole indication of preventing JRP or vertical transmission [6,81,94]. Cesarean delivery is indicated if vulvar or vaginal warts obstruct the birth canal, as the lesions may avulse and hemorrhage or cause dystocia during an attempted vaginal delivery.

HIV infected and immunocompromised women — Patients who are immunocompromised are particularly prone to development of condyloma, and often develop bulky and/or extensive lesions requiring repetitive treatment. The prevalence of anogenital warts is higher in human immunodeficiency virus (HIV) positive patients, who often have more than one HPV type, as well as higher viral loads of HPV [100-104]. In one study, the cumulative incidence of genital warts was 33 percent in HIV-seropositive versus 9 percent in HIV-seronegative women [104]. In another study, HIV-1 seropositive Kenyan female sex workers were nearly eight times as likely to have genital wars compared with HIV-1 seronegative women [105].

Vulvar biopsy is indicated when warts are identified in immunocompromised women because high-grade intraepithelial neoplasia is more common in warty lesions in these patients [106,107]. In fact, high-oncogenic risk HPV types are detected in up to 50 percent of genital warts removed from immunocompromised individuals, but only occasionally in immunocompetent individuals. Patients with HIV who are known to carry HPV are also at increased risk of vulvar carcinoma in addition to cervical cancer, and should therefore have a thorough vulvar examination as part of routine gynecologic care [108]. However, the absolute risk of invasive vulvar cancer is low [104].

Following biopsy to rule-out intraepithelial neoplasia, we suggest that immunocompromised women initially self-treat their warts with imiquimod. Topical 5 percent imiquimod is effective in immunocompromised women [102], and may be more effective than traditional medical therapies and surgical treatment [109]. In observational studies, approximately one-third of patients (primarily male) on antiretroviral therapy treated with imiquimod achieved total clearance [110,111]. Women who cannot adhere to this outpatient therapy and those whose warts do not clear with medical treatment can be treated surgically. We prefer surgical excision to laser therapy, as the former allows pathologic analysis of removed tissue.

Complete and permanent remissions of HPV anogenital lesions have been achieved with topical, intralesional, or systemic administration of cidofovir in a number of case reports; however, no large controlled trials have been performed. Furthermore, it was teratogenic and embryotoxic in animal studies; there are no data from human pregnancies. (See "Cidofovir: An overview".)

Although most women with HIV will have regression of warts with treatment [104], recurrence is common after all therapies [110,112].

Involvement of the clitoris — We treat warts on the clitoris with the same therapies used on vulva warts. Surgical procedures on the clitoris should be performed by physicians with experience operating in this sensitive area.

POSTTREATMENT ISSUES

Supportive care — Use of sitz baths, mild analgesics (eg, acetaminophen), and loose clothing can relieve discomfort and aid healing. Postoperative pericare is important for prevention of wound infection and breakdown.

Sexual activity — Sexual activity may be resumed when the patient feels comfortable and after any operative sites have healed, but this may take several weeks. There is some indirect evidence that use of condoms may accelerate disease resolution when both partners have type-concordant human papillomavirus (HPV) infection [113-115].

Follow-up — There are no standards for surveillance following treatment for genital warts. Follow-up appointments are based on patient symptoms and satisfaction with treatment results. Most patients who develop recurrent or refractory disease are diagnosed within three to six months of therapy. Recurrence is more common in immunocompromised individuals; more frequent follow-up or self-monitoring is reasonable to allow early intervention in these patients.

Cancer screening — Women with anogenital warts should undergo cervical cancer screening according to standard guidelines. As discussed above, HPV types associated with anogenital warts usually are not the same as those associated with cervical carcinoma, but oncogenic HPV viruses are sometimes involved. (See "Screening for cervical cancer".)

If they have no history of vulvar dysplasia, they should be followed with vulvar exams at the time of scheduled cervical cancer screening, and counseled that new oral, vulvar, or vaginal warts should be evaluated by a medical professional.

Women with perianal warts or a history of receptive anal intercourse may be at increased risk of high-grade anal squamous intraepithelial neoplasia, but there is insufficient evidence to recommend screening anal cytology [28]. (See "Anal squamous intraepithelial lesions: Diagnosis, screening, prevention, and treatment", section on 'Who should be screened for anal SIL?'.)

A population based study from Denmark including approximately 33,000 women with genital warts reported increased risks of cancer of the head and neck (standardized incidence ratio [SIR] 2.8), vagina (SIR 5.9), anus (SIR 7.8), and vulva (SIR 14.8) during a 10-year follow-up [116]. The increased risk of cancer could be related to HPV or due to differences unrelated to HPV between individuals with warts and the general population. This study is not sufficient to deviate from standard cancer screening guidelines for these cancers, as described above and in individual topics on these cancers. (See "Chemoprevention and screening in oral dysplasia and squamous cell head and neck cancer".)

RESOURCES FOR PATIENTS AND CLINICIANS

- British Association for Sexual Health and HIV
- Centers for Disease Control and Prevention

SOCIETY GUIDELINE LINKS — Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Gynecologic infectious diseases (non-sexually transmitted)".)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Anogenital warts (The Basics)")
- Beyond the Basics topics (see "Patient education: Genital warts in women (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- The main indications for treatment of vulvovaginal warts are bothersome symptoms and/or psychologic distress. (See 'Indications for treatment' above.)
- The majority of genital warts are cleared by a course of medical therapy. No treatment is significantly superior to another or appropriate for all patients and all types of warts. If the patient has not responded to the initial therapy after 3 weeks or complete clearance has not occurred by 6 to 12 weeks, it is appropriate to switch to a different method. (See 'Overview of treatment and prognosis' above and 'Selection of treatment based on clinical setting' above.)
- Biopsy to exclude precancerous or cancerous lesions is not necessary routinely, but is indicated when warts are identified in immunocompromised or postmenopausal women, when the lesions are visually atypical, or when warts fail to respond to standard therapy. (See 'HIV infected and immunocompromised women' above and 'Postmenopausal women' above and 'Indications for pretreatment biopsy' above.)

Treatment

- For nonpregnant women with limited vulvar disease who can comply with self-therapy at home, we suggest imiquimod over podophyllotoxin as initial medical treatment (**Grade 2C**). Sinecatechins are a reasonable alternative. (See 'Self-administered therapy' above.)
- For nonpregnant women with limited vulvar disease who cannot comply with self-therapy or fail self-therapy, we suggest treatment with trichloroacetic acid (TCA) rather than cryotherapy (**Grade 2C**). (See 'Office based therapy' above.)
- For nonpregnant women with limited vulvar disease that does not clear with monotherapy, we suggest treatment with imiquimod in combination with TCA (**Grade 2C**). (See 'Office based therapy' above.) For nonpregnant women with limited vaginal disease, we suggest TCA for initial medical therapy (**Grade 2C**). Laser ablation is our preferred surgical approach as it is possible to reach into the vagina and the depth of treatment can be controlled. (See 'Limited vaginal disease' above.)
- For pregnant women with bothersome symptoms from vulvar or vaginal warts, we suggest treatment with TCA rather than cryoablation (**Grade 2C**). For treatment of potentially obstructive lesions, we suggest laser therapy rather than excision (**Grade 2C**). These therapies have no known fetal effects. (See 'Pregnant women' above.)
- For patients with extensive (>20 cm^2) and/or bulky disease, we suggest surgery as initial therapy (**Grade 2C**). Laser ablation is less destructive and less technically challenging than excision, and better tolerated than electrocautery. (See 'Extensive and/or bulky lesions' above.)

- For patients with recurrent disease, the same treatment that resulted in initial clearance of warts is repeated and is likely to be successful. For refractory disease, we suggest a surgical approach or a combination of intralesional interferon and TCA (**Grade 2C**). (See 'Recurrent disease' above and 'Refractory disease' above.)

- For immunocompromised women without extensive and/or bulky lesions, we suggest self-treatment with imiquimod as first-line therapy (**Grade 2C**). (See 'HIV infected and immunocompromised women' above.)

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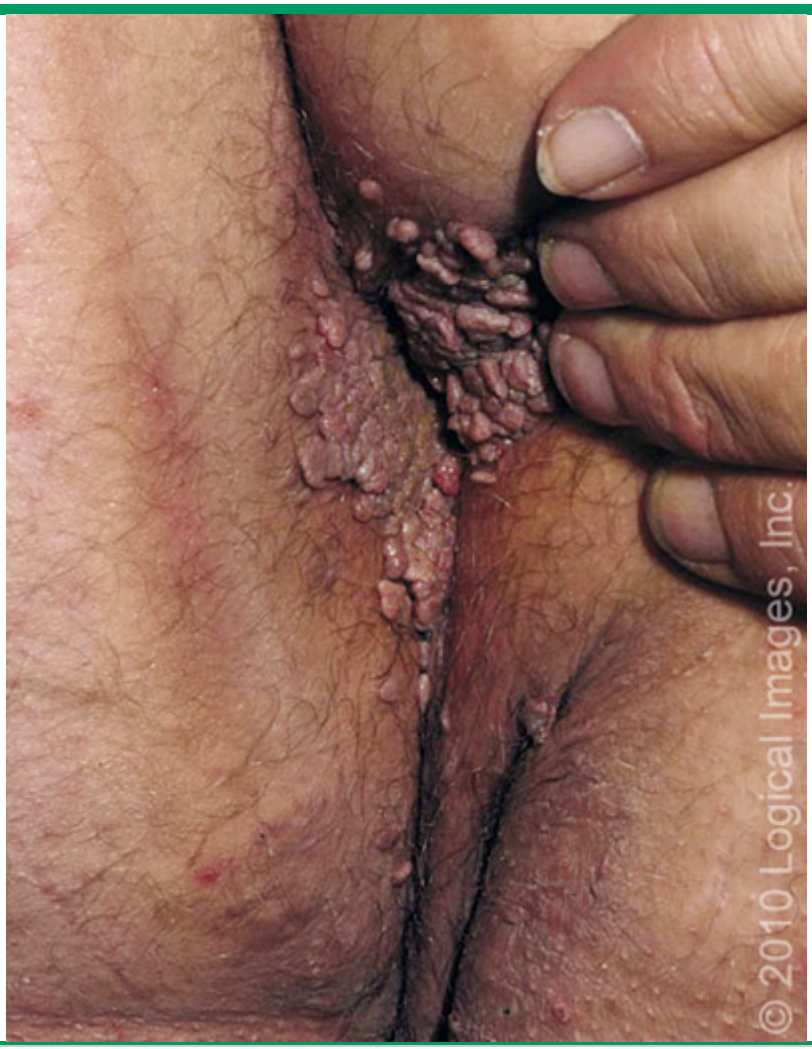
GRAPHICS

Perianal condyloma acuminatum



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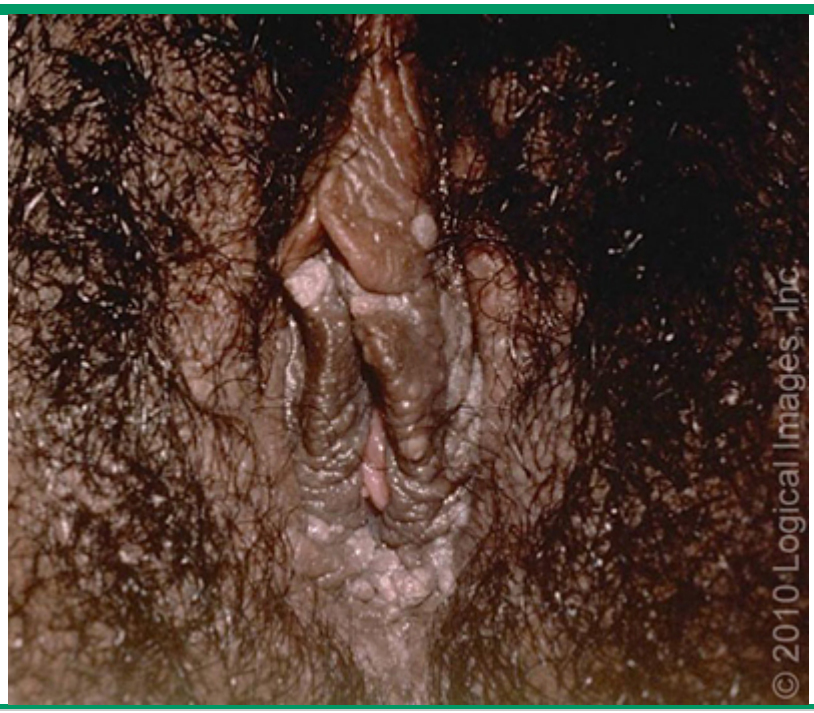
Vulvar condyloma acuminatum



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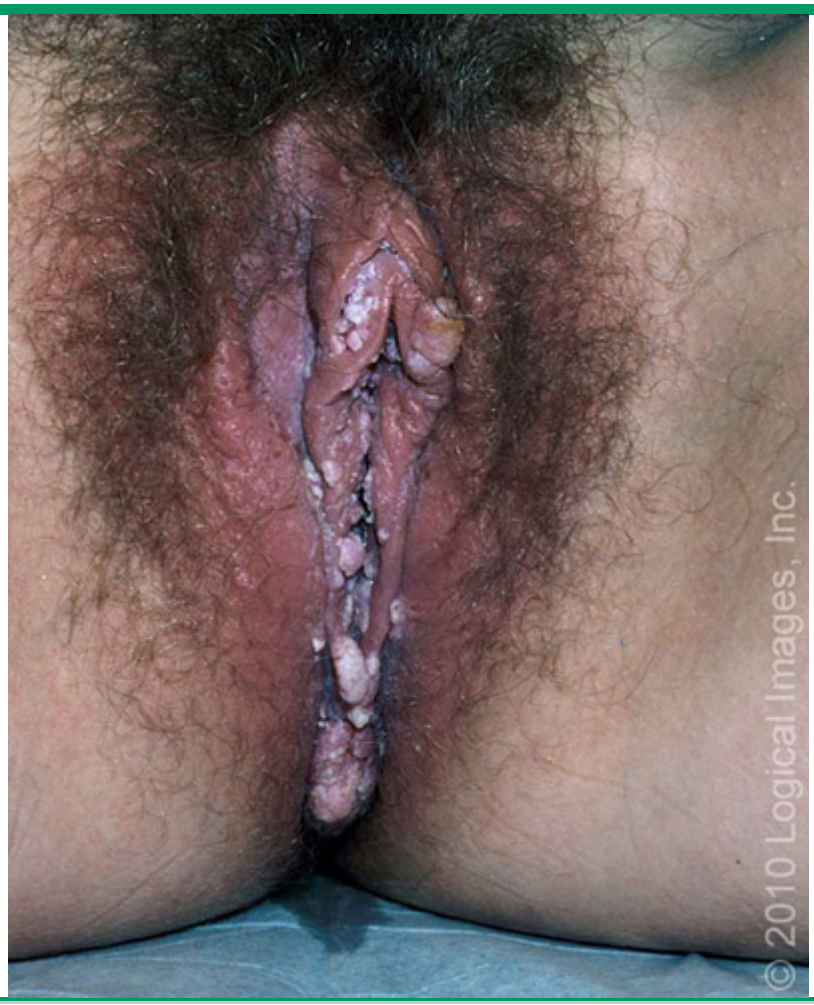
Condyloma acuminatum involving vulva, vagina, and perianal region



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Approach to the treatment of vulvovaginal warts

Self-administered therapies (vulva)
Podofilox 0.5 percent solution
Imiquimod 5 percent cream
Sinecatechins 15 percent ointment
Provider-admininstered therapies (vulva)
Without anesthesia
Cryotherapy with liquid nitrogen or cryoprobe
Podophyllin resin 10 to 25 percent in a compound tincture of benzoin
Trichloroacetic acid or bichloroacetic acid 80 to 90 percent
With anesthesia
Surgical removal (sharp, electrocautery, curettage, laser)
Therapies preferred for pregnant women (vulva)
Without anesthesia
Trichloroacetic acid or bichloroacetic acid 80 to 90 percent
Cryotherapy with liquid nitrogen or cryoprobe
With anesthesia
Surgical removal (sharp, electrocautery, curettage, laser)
Therapies preferred for treatment of vaginal warts
Without anesthesia
Cryotherapy with liquid nitrogen
Trichloroacetic acid or bichloroacetic acid 80 to 90 percent

Graphic 58922 Version 3.0

Contributor Disclosures

Daniela A Carusi, MD, MSc Nothing to disclose **Robert L Barbieri, MD** Nothing to disclose **Kristen Eckler, MD, FACOG** Nothing to disclose

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

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