MINI-REVIEW

# Female Genital Warts

**Fatemeh Ghaemmaghami[1], Zeinab Nazari[2], Nili Mehrdad[3]***

## Abstract

**Genital warts are a clinical manifestation of HPV types 6 and 11, and are estimated to affect 1% of sexually active adults aged between 15 and 49. HPV leading to a broad spectrum of human diseases, ranging from benign warts to malignant neoplasms, depending on the location of the lesion, the immune status of the patient and the type of HPV. Current therapies for human papillomavirus-associated disease are based on the excision or ablation of involved tissue and are associated with a high frequency of recurrent disease, discomfort and costs.**

**Keywords:** Genital warts - human papilloma virus - *Condyloma acuminata*

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## Introduction

In the last 50 years, changes in cultural and scientific realities and customs have resulted in a worldwide epidemic of sexually transmitted diseases (STD). Overwhelming examples of increasing and emerging STD pathogens exist in the early twenty-first century. These include HIV-1, the causative agent of acquired immunodeficiency syndrome (AIDS) and human papillomavirus (HPV) infections, the causative agents of genital warts and cervical cancer, with approximately 1 in 4 women harboring virus DNA in genital epithelium, 1-3 percent of women showing symptoms of infection and 250,000 deaths per year in women worldwide from cervical cancer; and numerous others (Howett et al., 2005).

In a cross-sectional study of 257 Indian women that included clinical, cytologic, colposcopic, and microbiologic screening of various gynecologic infections, HPV was the leading infection , affecting 127 (49.4%) women; however overt warts, were only seen in seven (2.7%) patients. Women infected with HPV had a 60.3-fold higher risk of developing a bleeding ectopia compared to those with other infections; women with an unhealthy cervix and cervical ectopias also had an increased risk of HPV infection (7.6- and 2.8-fold, respectively) (Singh et al., 1995). In a case series descriptive study of all sexually transmitted infections (STIs) diagnosed in Saudi Arabia from January, 1995 through December, 1999, the average annual incidence of STIs per 100,000 population for Saudis and non-Saudis, respectively, was as 1.4 and 0.7 for genital warts (Madani 2006). The magnitude of STD in the Eastern Mediterranean Region is not exactly known but is considered to be not insignificant (Ali et al., 1998). HPVs are associated with a variety of epithelial lesions, including benign genital warts and cervical intraepithelial neoplasia. Both causes significant morbidity in the general population, with cervical intraepithelial neoplasia progressing to cervical cancer in a subset of women who cannot resolve their infection (Doorbar et al., 2007).

## Risk factors

Transmission is believed to be predominantly through sexual intercourse, as genital HPV is absent in the majority of women who have not had sexual intercourse. There have been studies, however, that have detected HPV DNA in cervical or vulva-vaginal samples from women who have not had sexual intercourse. Transmission of HPV is enhanced when the superficial epithelium is disrupted, as this is where the infectious agent resides. The risk of transmission of HPV to offspring is also a concern. The increasing frequency of childhood genital warts has been proposed to be the result of sexual abuse. There may also be a non-sexual transmission of genital warts from mothers, as well as the possibility of transmission during passage through the birth canal if mothers have external or cervical genital warts (Gall, 2001).

Additional data support a vertical (transplacental) transmission of HPV DNA, as over 50% of children born to HPV 16 or 18 infected mothers were positive for these HPVs (Gall, 2001). Although the majority of sexually active adults will be infected with HPV at least once in their lives, it is sexually active women less than 25 years of age who consistently have the highest rates of infection. Besides youth and gender, common risk factors for HPV infection and clinical sequelae of infection include high number of sexual partners and coinfection with Chlamydia trachomatis or herpes simplex virus (Ault, 2006). Human immunodeficiency virus (HIV) infection is an additional determining factor for infection with other STDs,

*[1]Associate Professor, Gyneco-Oncologist [2]Fellowship of Gyneco-Oncology [3]Fellowship of Gyneco- Oncology, Medical Sciences/ Tehran University, Tehran, Iran *For Correspondence: Gyneco-oncolgist, Vali-E-Asr Hospital, Medical sciences/Tehran University, 2nd Floor Gynecologic Oncology Department, Vali-E-Asr Hospital Iran Fax: # 98-21-66937321 E-mail: nilimehrdad@yahoo.com*

including genital warts (Gall, 2001). Since the introduction of highly active antiretroviral therapy (HAART), opportunistic infections by bacteria and fungi have been reduced in HIV-positive patients. However, disease caused by HPV have become more frequent despite HAART. There is an increased incidence of condylomas and oral warts (Wienecke et al., 2006).

## Clinical presentation

Like many viruses, HPV is a fascinating organism. It is extremely difficult to grow in vitro; but once an individual becomes infected with HPV, it can be difficult or even impossible to eradicate. HPV is associated with mild to moderate disease that even in the absence of therapy may spontaneously regress. On the other hand, some HPV infections progress to cancer, which can be fatal if treatment is delayed (Carr et al., 2000).

Most HPV infections are cleared by the immune system and do not result in clinical complications. Clinical sequelae in cases of low-risk HPV infection consist of genital warts, and clinical manifestations of high-risk HPV infection include abnormal Pap test results, low-grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesions (HSIL), and cervical cancer (Ault, 2006). Genital warts (condyloma acuminatum, venereal warts) are common highly contagious benign epithelial lesions occurring on the genitals, perianal area, and inguinal folds, and are caused by human papillomavirus (HPV). Diagnosis is based largely on the clinical appearance of lesions (Brodell et al., 2007). The clinical manifestations of HPV infection depend on the viral subtype, the immune status of the patient, and environmental co-carcinogens. Infection with HPV is often asymptomatic, which makes viral detection challenging (Zanotti et al., 2002). The main manifestations of anogenital warts are cauliflower-like condylomata acuminata that usually involve moist surfaces; keratotic and smooth papular warts, usually on dry surfaces; and subclinical "flat" warts, which can be found on any mucosal or cutaneous surface (Handsfield, 1997).

The lesions can be flat, dome-shaped, keratotic, pedunculated, and cauliflower-shaped; they may occur singularly, in clusters, or as plaques (Wiley et al., 2002).

Warts are not exclusive to external genital tissues. Sexual exposure can be associated with warts in the urethra and at the meatus, cervix, vagina, anus, and oral cavity. Cervical warts, however, require clinicians to rule out high grade dysplasia using Papanicolaou tests prior to treatment (Wiley et al., 2002). EGWs can be diagnosed through direct visual inspection with bright light and magnification. Biopsy is not routinely recommended. However, when EGWs are not responsive to therapy or when neoplasia is suspected because of blue or black discoloration, sudden recent growth or fixation to underlying structures, biopsy and histological evaluation should be performed (Wiley et al., 2002). Biopsy, Viral typing, acetowhite staining, and other diagnostic measures are not routinely required (Kodner et al, 2004). The differential diagnosis for external genital warts includes a number of skin conditions: condyloma latum, seborrheic keratoses, dysplastic and benign nevi, molluscum contagiosum, and neoplasms. Condyloma latum is due to secondary syphilis, an infection caused by Treponema pallidum, and can be diagnosed with dark- field microscopy and standard serological tests for syphilis (Wiley et al., 2002). Seborrheic keratoses are common, localized hyperpigmented lesions that are rarely associated with malignancy. Molluscum contagiosum is caused by a poxvirus, highly infectious and common in immunodeficiency; lesions are usually umbilicated. High-grade intraepithelial lesions and cancers that may mimic genital warts include: Bowen's disease, Bowenoid papulosis, squamous cell carcinoma, Buschke-lowenstein's tumors, vulvar intraepithelial neoplasias (VINs) and dysplastic nevi (Wiley et al., 2002).

## Laboratory tests

Sadan et al. found an association between exophytic vulvar condyloma acuminata and abnormal pap smear or positive cervical biopsy, in generally healthy women (Sadan et al., 2005).

To determine the value of cytology in detecting mature and immature papillary condylomas of the uterine cervix, Pinto et al. evaluated 23 papillary condylomas by pap smear and biopsy and classified histologic sections according to maturity and keratinization. Corresponding smears were cytologically diagnosed as LSIL (6, 26%), atypical squamous cells of undetermined significance (7, 30.4%) and negative (10, 43.4%). Careful cytologic review diagnosed only two of the 13 mature lesions; few cytological criteria of LSIL and HPV infection were observed. Koilocytes were seen in just 1 case. Sample limiting factors occurred in 4 cases: 2 cytologically diagnosed as LSIL, 1 as ASCUS and 1 as negative for lesion. They concluded that cytology was not effective in the detection of cervical condyloma accuminatum independent of limitations in sample adequacy and of degree of maturity or keratinization of the lesions (Pinto et al., 2007). There are no data to suggest that molecular testing for nucleic acids (e.g., hybrid capture assays) are effective and they are not recommended in the routine diagnosis or management of external genital warts (Wiley et al., 2002).

## Condylomata acuminata during pregnancy

Genital warts often increase in size during pregnancy and can pose some problems in the therapeutic management on one hand; vaginal labor can expose the new-born baby to the risk of contamination with HPV (estimated at 4%) on the other hand (Ouerhani et al., 2006). In Gajewska's study evaluating the correlation between maternal HPV infection and HPV presence in the cord blood and the oral cavity of the neonate, HPV was found with 26% pregnant women. High percentage of HPV transmission from mother to neonate was obtained. There's a suggestion that HPV infection of fetus may occur in utero (Gajewska et al., 2006).

To avoid exposure to the virus, delivery by cesarean section has been proposed by some. However only a very

limited cost- benefit analysis has been performed, and the true effectiveness of this procedure is unknown (Wiley et al, 2002). In addition, the morbidity associated with cesarean section is significant and, when conservative estimates are used, the risks associated with cesarean section are greater than the risk of rearing a child with Juvenile Onset Recurrent Repiratory Papilomatosis (JORRP) (Wiley et al., 2002). Thus cesarean section is not recommended for prevention of JORRP (Wiley et al., 2002).

## Prevention

Although the behavioral profiles typically associated with an increased risk for STI (including lifetime partner number, age at first intercourse, and so forth) will certainly lead to an increased risk for HPV detection, there is a high absolute prevalence of HPV even among women who have few lifetime sex partners. Examination of sex partners is not necessary for the management of external genital warts, because there are no data indicating that reinfection from untreated partners plays a role in recurrences. However, partners of genital warts affected patients may benefit from examination to assess the presence of genital warts, from STD and Pap smear screening (Wiley et al., 2002). Condoms may provide some protection against HPV-related diseases and thus are recommended in new sexual relationships and when partnerships are not mutually monogamous (Wiley et al., 2002).

It could be argued that to counsel patients for an HPV infection as an STI would be counterproductive, as short of absolute abstinence, the prevention of infection is difficult and treatment options, short of excisional procedures for neoplasia, are limited. The real promise held in this area is the availability of an apparently highly effective prophylactic HPV vaccine, targeting at least HPV 16, 18, 6, and 11 (Gravitt et al., 2005).

Within the spectrum of therapeutic options for condylomata, no method is really superior to others; recurrences occurred in 30-70% of cases. We definitely need the HPV vaccination programme to get rid of one of the oldest and up to now unsolved problems of mankind (Schneede et al., 2006). This vaccine cocktail, if it achieved 100% coverage, could theoretically prevent 50% to 70% of invasive cervical cancers and most genital warts. Vaccination will be required among women before initiation of sexual contact, presumably among girls 10 to 13 years of age (Gravitt et al., 2005). The challenges of the journey from target identification through development of a prophylactic quadrivalent human papillomavirus (HPV) vaccine have been met in Gardasil. The quadrivalent HPV vaccine was generated by expression of the major capsid protein (L1) of HPV types 16, 18, 6 and 11 in yeast. L1 proteins self assemble into pentamer structures and these pentamer structures come together to form virus-like particles (VLPs). The VLPs are antigenically indistinguishable from HPV virions. The VLPs contain no viral DNA and therefore the vaccine is non-infectious. Gardasil is composed of VLPs of HPV types 16, 18, 6 and 11 conjugated to a proprietary amorphous aluminum hydroxyphosphate sulfate adjuvant. The results of a rigorous clinical program have demonstrated that the vaccine is safe and highly efficacious in preventing dysplasias, cervical intraepithelial neoplasias (CIN 1-3) the precursors of cervical cancer and external genital lesions caused by vaccine-HPV types. In conclusion, Gardasil addresses a major medical need, that is, reduction of HPV-related disease including cervical cancer as a safe, immunogenic, and highly efficacious vaccine (Bryan, 2007).

## Treatment

Genital warts are not only unsightly, but the treatment may also be complex and the results of such treatment variable. For the patient this may result in physical and psychological trauma. The nurse can provide the patient with the physical and psychological support the patient needs only if he/she has insight and understanding regarding the infection, its natural history, the diagnosis and subsequent management. Care should be provided in a non-judgmental manner, with respect and empathy (Peate, 2006). A routine screen for sexually transmitted infections is appropriate in most cases (O'Mahony, 2005).

Some evidence exists that treatment reduces infectivity, but there is no evidence that treatment reduces the incidence of cervical and genital cancer (Kodner et al., 2004). Treatments are aimed at eradicating the unsightly lesions and stimulating the immune system to generate clearance and prevent recurrence (O'Mahony, 2005). There are many current treatments for genital warts; however, none are successful in all three goals of therapy: complete eradication of warts, maintaining clearance and eliminating the virus (Gall, 2001). Not all genital warts therapies have been studied and not all are available in every treatment setting. Recurrences are common, and there is no single treatment that is superior to others (Wiley et al., 2002). Treatment options for genital warts are numerous, well established, and effective. Topical treatments include podophyllin resin, imiquimod, trichloroacetic acid, and podophyllotoxin. Surgical or destructive therapies include carbon dioxide laser, surgical excision, loop excision, cryotherapy, and electrodessication. Interferon can be injected locally or administered systemically to treat genital warts (Scheinfeld et al., 2006). Podofilox, imiquimod, surgical excision, and cryotherapy are the most convenient and effective options. Fluorouracil and interferon are no longer recommended for routine use (Kodner et al., 2004). Evidence of efficacy in the treatment of genital warts is drawn from randomized blind-controlled trials, prospective studies, and retrospective cohort studies. Evidence of efficacy appears to be good, but more head-to-head studies and comparisons of combination therapies versus monotherapy need to be done. Treatment of choice depends on the number, size, and location of lesions. There is little certainty that any approach is more effective than another, however costs differ. It would seem that the first line destructive treatment is cryotherapy, but surgery and electrodesiccation are more effective. The first line topical treatments appear to be podophyllotoxin and imiquimod.

Interferon is too expensive and trichloracetic acid is too inconsistent to be recommended as primary treatment. It is unclear if combinations of therapies are more effective than monotherapy. Side effect profile, cost, effectiveness and convenience define the choice of therapy (Scheinfeld et al., 2006). However, many patients respond extremely well to home therapies with either podophyllotoxin or imiquimod. Patients prefer the comfort and dignity of home treatment, and this should be the first-line of treatment for the majority of patients (O'Mahony, 2005). Home therapy should be reserved only for initial therapy of simple cases. Such approaches include podophyllotoxin solution, podophyllotoxin cream, imiquimod cream and adjuvant interferon gel (Table 1). Recurrent disease and disseminated disease must be treated by the physician. Choice of therapy depends on the morphology, the extent of the disease and also on the immunological status of the patient. Whatever therapy will be chosen, HPV DNA can persist latently in surrounding tissue and may lead to recurrence of visible lesions. Long-standing warts can undergo malignant conversion; intraepithelial neoplasias such as Bowen's disease, erythroplasia of Queyrat and bowenoid papulosis are especially prone to develop into squamous-cell carcinoma. Thus adequate therapy and thorough follow-up are mandatory in such cases. In the future therapies directed against HPV specifically will be available (Gross, 2001). They should lead both to destruction and complete clearance of visible lesions and also should prevent recurrences. Ideally HPV should be eliminated completely from the treated tissue (Gross, 2001).

Nonsurgical provider-prescribed and -applied therapies include: podophyllin resin, interferon (IFN) and bi-and tri-chloroacetic acid (BCA/TCA). Patient–applied nonsurgical treatments include: podophyllotoxin (podofilox) solution, podophyllotoxin cream, imiquimod cream (aldara), 5-fluorouracil (5-FU) cream and interferon gel. The use of nonsurgical treatment is contraindicated when there is any history of hypersensitivity to any product constituent (Wiley et al., 2002). Wilson et al. evaluated the factors involved in clearance of genital warts. In their study, the number of treatment episodes, and number of weeks, to clear the warts were documented. Number of warts and wart area at presentation were associated with time and number of treatments to clear. Those with 1-3 warts required significantly fewer treatment episodes and less time to clear than those with 11-41 warts, as did those with warts area 2-19 mm2 compared with wart area 100-1038 mm2. Using survival analysis, the number of warts was significant for the number of treatments and weeks to clear. The clearance rates in non-smokers compared with smokers were higher, but not significantly different (Wilson et al., 2001). Wart burden at presentation is an indicator of time to clearance. The number of warts is the best predictor -fewer warts results in earlier clearance (Wilson et al., 2001). Home treatment with podophyllotoxin or imiquimod are commonly prescribed therapies for anogenital warts. It is important to ascertain if patients are locating all lesions for treatment and if they know when they are clear of them. Carey et al. set out to assess patients';Òbm\ity to determine the number and location of their genital warts and compare their observation with that of their examining doctor or nurse (Carey et al., 2004). Following instruction on the use of home treatment and being given an instruction leaflet patients were reviewed in four weeks' time. 155 patients enrolled in the study 31% (48) male, 69% (107) female. At initial assessment 62.5% (30) of male patients and 59.8% (64) of female patients underestimated the extent of their disease: 10.5% (5) of male patients and 10.3% (**11**) of female patients overestimated their disease burden with some mistaking skin tags for genital warts. Patients undertaking home treatment for warts not only need detailed instruction on its use but should be reviewed to assess the success of treatment (Carey et al., 2004).

Trichloroacetic acid is a widely used non-surgical therapy, but little is known about its efficacy, and it is associated with unpleasant side-effects. The patient-applied treatments imiquimod and podophyllotoxin are newer therapy choices which are more acceptable to both patients and practitioners. The wart clearance rates for these two treatments are similar, although imiquimod is associated with lower recurrence rates (Maw, 2004).

Podopyllotoxin/ podofilox: Podophyllotoxin solution 0.5%, approved for patient self-administration, has been used most extensively in the treatment of genital warts (Yan et al., 2006). podofilox is an antimitotic agent that destroys warts by inducing tissue necrosis locally (Table 2). Podofilox is supplied in 0.5% gels, solutions and creams and generally is applied twice daily for 3 consecutive days and repeated for 2-4 cycles (Wiley et al., 2002). Placebo-controlled trials have shown that 45%-77% of patients attained clearance within 4-6 weeks of treatment (Table 1). Commonly reported side effects due to podofilox include local inflammation or irritation, most often erosion, burning, pain, and itching. Symptoms uncommonly associated with podofilox include dyspareunia, bleeding, scarring and insomnia. Recurrences have been reported for 4%-38% of patients followed in clinical trials. Safety during pregnancy has not been evaluated; effective contraception for women of childbearing age is advised (Wiley et al., 2002). Claesson et al. evaluated the efficacy and safety of a cream formulation of podophyllotoxin at 2 concentrations 0.15% and 0.3%, using 0.5% podophyllotoxin solution as a reference treatment. The results of their study showed that there were no statistically significant differences between the 3 treatments with regard to both efficacy and safety (Claesson et al., 1996). Lacey et al. evaluated the efficacy and cost effectiveness of self applied podophyllotoxin 0.5% solution and podophyllotoxin 0.15% cream, compared to clinic applied 25% podophyllin in the treatment of genital warts over 4 weeks (Lacey et al., 2003). They conducted a randomised controlled trial in 358 immunocompetent men and women with genital warts of 3 months' duration or less. In the principal analysis both podophyllotoxin solution (OR 2.93, 95% CI 1.56 to 5.50) and podophyllotoxin cream (OR 1.97, 95% CI 1.04 to 3.70) were associated with significantly increased odds of remission of all warts compared to podophyllin. Local side effects were seen in 24% of subjects, and recurrence of warts within 12 weeks of study entry in 43% of all

**Table 1. Typical Treatment Cycles for Patients with Genital Warts**

| Treatment | Typical cycle |
|---|---|
| *Patient- applied treatments* | |
| Imiquimod (Aldara) | apply at bedtime for 3 days, then rest 4 days; alternatively may apply every other day for 3 applications, may repeat weekly cycles for up to 16 weeks |
| Podofilox (condylox) solution or gel | apply twice daily for 3 days, then rest 4 days ; may repeat for 4 cycles |
| *Physician- applied treatments* | |
| Cryotherapy | use liquid nitrogen or cryoprobe; repeat every 1 to 2 weeks, if necessary |
| Interferon | not recommended for use |
| Podophyllin resin | apply to each wart and allow to dry; may be repeated weekly if necessary |
| Tricholoroacetic acid | apply a small amount to warts and allow to dry; repeat weekly, if necessary |

initially cleared subjects, without statistically significant differences between the treatment groups. Costs were similar across the three treatment groups. They concluded that self treatment of anogenital warts with podophyllotoxin showed greater efficacy and cost effectiveness than clinic based treatment with podophyllin (Lacey et al., 2003).

*Imiquimod (Aldara)*

Immunomodulators have been used for some time in various medical specialities, but have only recently been used in gynaecology. The first drug in this therapeutic class, Imiquimod (Aldara), has been shown to be effective in treating lesions induced by Human Papillomavirus (HPV) such as genital warts or cervical and vulvar dysplasia, by stimulating the immune system of an infected individual. Thanks to its ease of use and its few side effects, Imiquimod would appear to be, in the future, the treatment of choice for these types of viral infections, alone or in association with therapeutic vaccines or physical ablative therapies as a prevention of relapses (Baulon et al., 2007). (Table 1)

Imiquimod is applied topically, and both 1% and 5% preparations have been studied; 5% cream is more efficacious and has been approved for genital wart treatment by FDA (Wiley et al., 2002). In 3 randomized placebo-controlled trials of 5% cream, 37- 54% of treated patients showed clearance within 16 weeks (Wiley et al,. 2002). Imiquimod is dispensed as an individual dose and is applied directly to the affected area at bedtime, 3 times/ week for up to 16 weeks. Patients are advised to wash the affected area with mild soap and water on awakening, to remove residual drug (Wiley et al., 2002). Recurrences have been reported in 13-19% of clinical trial subjects who were treated with 5% imiquimod cream . Safety during pregnancy has not been tested; effective contraception is advisable for women of childbearing age (Wiley et al., 2002). 0.5% podophyllotoxin and 5% imiquimod have not been compared in any extensive and formal studies, although they are the common topical agents for genital warts (Yan et al., 2006). To evaluate the efficacy and safety of topical 5% imiquimod and 0.5% podophyllotoxin in the treatment of genital warts, Yan et al. collected the randomized controlled trials of 5% imiquimod and 0.5% podophyllotoxin in the treatment of genital warts. The clinical cure rates of imiquimod and podophyllotoxin were 50.34 and 56.41%, respectively, without statistically significant differences between the two ($p > 0.05$). A combined analysis of the 3 studies on imiquimod showed a statistically significant difference to the placebo group [pooled odds ratio (OR) 11.65, 95% confidence interval (CI) 6.05-22.44], as did a combined analysis of the 9 studies on podophyllotoxin (pooled OR 16.70, 95% CI 7.06-39.48). The most common adverse events of imiquimod were erythema, erosion, excoriation, itching and burning; those of podophyllotoxin were burning, pain, erosion, itching and inflammation. They concluded that Imiquimod and podophyllotoxin possess similar curative effects on condylomata acuminata but podophyllotoxin has more serious adverse effects (Yan et al., 2006). Lafuma et al. compared the costs and the efficacy of treatment of external anogenital warts with imiquimod and podophyllotoxin and laser therapy in the case of failure or relapse. A model simulating the two successive treatments was built. In the first phase, the two topical treatments applied by the patients: podophyllotoxin for 4 weeks and imiquimod for 16 weeks were compared. In the case of failure or relapse, laser therapy was applied. Imiquimod provided a clearance rate of 49.5 p. 100, i.e., the disappearance of the lesions at 16 weeks, greater than that of podophyllotoxin (28.3 p. 100) at 4 weeks. The relapse rate was lowest with imiquimod (13.3 p. 100) than with podophyllotoxin (30.9 p. 100). Imiquimod, because of its greater initial efficacy, is at least as cost-effective as podophyllotoxin the treatment of external genital warts (Lafuma et al., 2003).

Cox reported the case of a 21-year-old female with extensive genital warts. A patient-applied, non-destructive therapy was considered to be the most appropriate treatment in this case, due to the extent of the disease and the resulting psychological distress experienced by the patient. She applied imiquimod 5% cream three times per week for a period of 5 weeks, which resulted in complete clearance of all the warts. Minor inflammatory changes were observed during treatment; however, no significant pain was by reported the patient. No recurrences were reported during 2 years of follow-up (Cox 2003).

*Podophyllin resin*

Podophyllin resin is an antimitotic agent that, like podofilox, destroys warts by inducing tissue necrosis locally (Table 2). It is compounded as a 10%-25% suspension in tincture of benzoin; to avoid the risk of systemic absorption and possible toxicity, podophyllin should not be used for areas >10 mm2 . A variety of adverse effects including bone marrow suppression,

hepatocellular dysfunction, neurological compromise, hallucinations, psychosis, nausea, vomiting, diarrhea and acute abdominal pain have been reported over the past 20 years. Recurrences have been reported for 23%-65% of clinical trial participants and it is not safe during pregnancy (Wiley et al,. 2002).

*BCA/ TCA*

The acid denatures and precipitates proteins and kills genital wart-affected tissues. Although BCA/TCA has rarely been studied, it is widely used in practice. Treatment concentrations are not standardized, but early studies reported the use of 85% and 95% concentrations (Wiley et al., 2002). BCA/TCA may run onto adjacent, healthy skin if overapplied. Applying carefully and allowing drying time afterward will prevent the spreading of acid on to unaffected areas. Local pain, ulceration, and scabbing have been reported (Wiley et al., 2002).

*Pegylated interferon alfa-2b*

Interferon in a variety of topical, interlesional, and parenteral preparations has been used for condylomata acuminata (CA) in HIV negative patients. Brockmeyer et al. initiated an open trial to determine the safety and efficacy of a new formulation of interferon, pegylated interferon-alpha2b (PEG-IFN, PegIntron) in the treatment of recalcitrant CA in patients with HIV infection. 22 HIV-1 infected patients in virologic steady state with clinically demonstrable anogenital CA were enrolled in this study (treatment group, n=12; control group, n=10). Patients in the treatment group received 80 microg PEG-IFN s.c. once a week for 24 weeks. Follow-up period was 6 month. 2 patients did not finish the study because of side effects (Brockmeyer et al., 2006). PEG-IFN was well accepted and completed by ten patients. Four patients revealed complete response, four patients had major response and two had minor response after PEG-IFN. In the control group, all patients showed progression of CA during the 24 weeks of this study ($p < 0.001$). 7/10 patients of the treatment group and 8/10 patients of the control received HAART. Biological side effects of PEG-IFN treatment included flu-like symptoms, fatigue, local reaction, leukopenia, and increase of AST. PEG-IFN is an effective and safe therapy option in HIV infected individuals with CA with concomitant positive effects on the suppression of HIV-1 replication and CD4 cell count. It might be considered as an alternative in patients that have failed to standard therapies of CA and - at the same time -could improve the benefit of HAART to a great extent. This last hypothesis needs further research (Brockmeyer et al., 2006).

**Table 2. Mechanisms of Selected Treatment Options for Genital Warts**

| Treatment | Mechanism of action |
|---|---|
| Cryotherapy | Destruction by thermal- induced cytolysis |
| Imiquimod (Aldara) | Cell- mediated immune response modifier; induces interferon production |
| Interferon | Antiviral, antiproliferative, and immunomodulatory activity |
| Podofilox (Condylox) Solution or gel | Cytotoxic, antimitotic, major biologically active component of pedophillin resin |
| Podophyllin resin | Cytotoxic, antimitotic (causes tissue necrosis) |
| Trichloroacetic acid | Protein coagulation of wart tissue |

*Surgical treatments*

According to guidelines of the German STD Association, appropriate treatment of extensive anogenital warts with comparable recurrence rates includes cryotherapy, surgical excision, electrosurgery, Co2 and Nd:YAG-laser vaporization. All these procedures are associated with varying degrees of risk for bleeding, release of potentially infectious aerosol, deep thermal destruction, slow wound healing, and scarring (Weyandt et al., 2005)

Surgical treatments directly ablate or excise wart affected tissues, using curettage or tangential excision, electrocautery, or electrotherapy (Table 3). Genenrally, anesthesia, analgesia and infection control are priorities with all surgical treatments. The resulting surgical wound for most genital wart excisions, if performed properly, should extend only in to the upper regions of the dermis (Wiley et al., 2002).

*Surgical excision*

Surgical excision that uses scalpel, curettage, or scissors directly removes wart affected tissues. Ghaemmaghami et al. reported a 45-year-old woman presenting with a huge mass on her external genitalia unresponsive to local medical treatments including podophyllin solution and TCA (Fig 1). Multiple biopsies detected ordinary condyloma acuminatum and neither malignancy or cytological atypia was detected. Wide surgical excision was performed. The postoperative course was uneventful and the cosmetic result was satisfactory (Ghaemmaghami et al., 2007). Podophyllin resin appears to be less effective than surgical excision, however, when compared with laser therapy, surgical excision is about equally effective (Wiley et al., 2002)

*Electrosurgery*

Electrosurgery uses electrical energy, in the form of

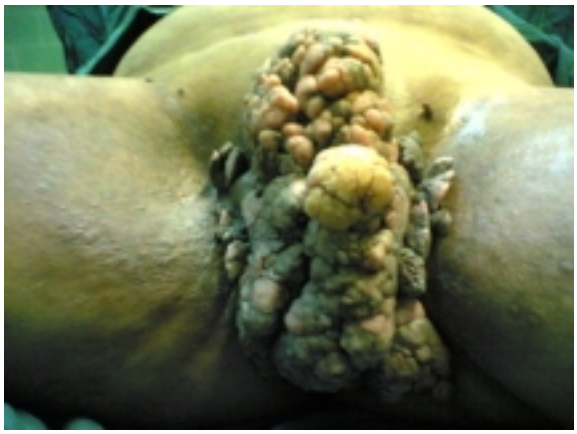
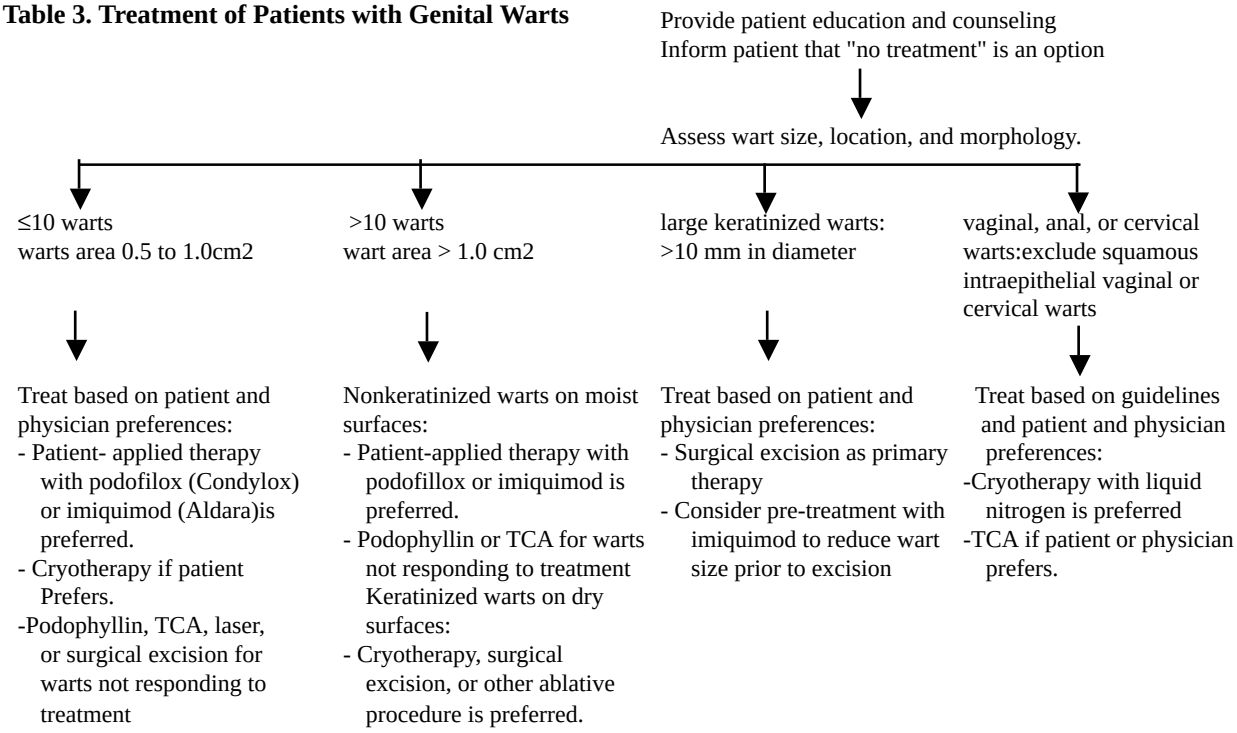


**Figure 1. Giant Condyloma Accuminatum**

**Table 3. Treatment of Patients with Genital Warts**




thermal coagulation or electrocautery, to destroy external genital warts affected tissues (wiley et al., 2002). Compared with podophyllin resin, electrotherapy is about twice as effective initially but equally effective 3 months after therapy. Two randomized trials showed slightly greater efficacy for electrotherapy compared with cryotherapy; however, the differences in outcome is only short term and does not persist after 3 months of follow up (Wiley et al., 2002).

*Cryotherapy*

The temperature of -80 degrees C which can be obtained using hyperdry nitrogen monoxide equipment allow radical treatment to be performed without pain in an outpatient setting without general or loco-regional anesthesia (Table 1). The characteristics of this treatment allow patients to be regularly monitored, thus eliminating all signs of recidivation of those lesions which were too small to be seen at the start of treatment. The patient is considered cured after an interval of approximately 30-40 days after the disappearance of all condylomas (Cordellini et al., 1991).

*Laser therapy*

Carbon dioxide laser vaporization of condyloma acuminata continues to be the treatment with a greater rate of success and with excellent cosmetic results. In a clinical prospective study, Padilla-Ailhaud evaluated the clinical outcome of carbon dioxide laser vaporization of condyloma acuminata at a referral center in Mexico. Carbon dioxide laser vaporization was performed for condyloma acuminata in 46 women and 35 men, measured from 3 to 60 months with colposcopy or peneoscopy every 6 months. The women's study follow-up showed an initial success rate of 93%, and the recurrence rate after 6 months of treatment was 7%. The follow-up of men showed an initial success rate of 69%, and the recurrence rate after 6 months was 25%. The success rate in women after the second treatment was 100% without recurrence. In men, the second treatment success rate was 88%, and the recurrence rate after 6 months was 33% (Padilla-Ailhaud, 2006).

Laser therapy uses focused, infrared light energy to vaporize external genital warts affected tissues. Laser treatment is more complex and costly than other surgical treatments such as cryotherapy and electrosurgery and requires specialized equipment and additional clinical training to perform properly. Although some specialists offer laser treatment as an in-office procedure, there are circumstances in which in-hospital treatment and general anesthesia are indicated. For example if external genital warts are extensive and the treatment field is large, in-office laser treatment may not be feasible. The efficacy of laser treatment ranged from 23% to 52% for studies where follow-up ranged from 3 to 18 months.

Post surgical procedure management include sitz baths, use of warm water, that may aid in healing and minimize secondary irritation. After cleansing, heat sources (e.g. heat lamps and warm air from hair dryers) can be useful to aid in healing and alleviate discomfort. If heat lamps are used, they should be placed no closer than 18 inches from the prigenital region; low-wattage bulbs (e.g. 45-60 watt bulbs) and fewer than 10-15 min of use several times daily are advisable, if patients use hair dryers to dry the affected area, the dryer should be held ≥18 inches from the affected area, and heat should be adjusted to the lowest possible heat setting. In an open clinical trial made up of 208 evaluable patients, Ferenczy et al. assessed the technical characteristics, side effects, complications, and effectiveness of electrosurgery vs continuous wave CO2 laser in the treatment of genital warts. To avoid selection bias, in each patient half of the lesions measuring 2 cm2 or greater total linear area were treated with loop electroexcision and ball electrofulguration, and the other

half were treated with CO2 laser excision and vaporization in a continuous wave mode spot welding. The average operative time was 6 min for electrosurgery and 8 min for laser. Healing was completed in 95% of patients with a lesional area of 5 cm2 or less and 100% of patients with 5 cm2 or larger by the third and sixth postoperative week, respectively. Severe discomfort occurred in 12% of patients, and 4% of patients developed delayed complications, including vitiligo and scarring, irrespective of treatment modalities used. Complete clearance of warts after a single and multiple treatments were similar in areas treated with electrosurgery and CO2 laser. Electrosurgery appeared to be as effective as continuous wave CO2 laser for treating vaginal and external anogenital condylomas, particularly those limited to a 5 cm2 or less area (Ferenczy et al., 1995)

In a cross-sectional survey, data relating to management of anogenital warts (AGW) during a single-patient visit only at genitourinary medicine clinics were collected (McClean et al., 2005). Single-agent use of cryotherapy, podophyllotoxin and trichloroacetic acid (TCA) were the most common treatment modalities, accounting for over two-thirds of all modalities used. Podophyllin, alone or in combination with other agents, was used for about 20% of first-line treatments. Podophyllin was included in about 15% of all treatment modalities. Guidelines for the management of AGW continue to recommend the use of podophyllin, but this may need to be modified in the light of recent publications. Podophyllin, TCA, podophyllotoxin or combinations of these agents are commonly used to treat keratinized warts. About 11% of all treatments involved a combination of two or more agents (McClean et al., 2005).

*Argon-plasma coagulation*

Using argon-plasma coagulation anogenital warts can be removed in layers in a controlled manner. High frequency current flows through the argon plasma to the tissue, allowing well-controlled, superficial tissue destruction (Weyandt et al., 2005). Compared to other therapeutic procedures, argon-plasma coagulation is a better controlled, quick and low-risk option for the treatment of anogenital warts. Depending on the type of involvement and individual risk factors, postoperative treatment with topical imiquimod cream may be useful (Weyandt et al., 2005).

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