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CONTINUING PROFESSIONAL DEVELOPMENT

Treatment of genital warts — what's the evidence?

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Summary: Genital warts are usually asymptomatic, and rarely cause discomfort. Once the patient is aware of them the main symptom is their cosmetic appearance and resultant psychological consequences. The ideal treatment outcome would be complete viral eradication, but this is not possible. Treatments focus on the removal of exophytic warts, leaving the surrounding subclinical and latent human papillomavirus (HPV) infection as areas of possible transmission and recurrence. Effective treatment does reduce HPV viral load, so the infection is reduced if not completely eradicated. Treatment is often painful, inconvenient, and may produce poor clearance rates and frequent recurrences. The treatment chosen should be no worse or more dangerous than the disease itself, and should be tailored to the patients' disease and needs as well as to the available resources. Genital warts are highly infectious and sexual partners may well already be infected when a patient presents for treatment. There are no published studies showing that condom use reduces transmission of HPV from people with genital warts. However, if the sexual partner is uninfected; using a condom may protect against HPV lesions and genital warts. Condom use should be encouraged in new relationships.

Keywords: genital warts, treatment

DEFINITION

Genital warts are mainly due to HPV 6 with some HPV 11. These viral subtypes can cause latent infection, subclinical infection and clinically apparent benign warts and low-grade cervical intraepithelial neoplasia (CIN).

This article only covers the treatment of genital warts, i.e. exophytic lesions of the anogenital tract that are visible with the naked eye, including condylomata acuminata and papular warts. It does not cover treatment of subclinical infection that is only visible with acetic acid and/or colposcopy nor latent infection identified by HPV DNA detection.

PREVALENCE AND INCIDENCE

Genital warts are the most common sexually transmitted infection (STI) in the USA and Europe. A cohort study of HIV-negative women in the USA reported a baseline prevalence of genital warts in 1.2%. The incidence was 0.8 per 100 person years follow-up[1]. In 1999 there were 61,559 new patient presentations with genital warts to genitourinary medicine clinics in England[2]. First attack, recurrent and re-registered cases of genital warts accounted for 21% of all diagnoses made. Genital warts therefore constitute a large proportion of the workload of clinics treating STIs, so rationalization of treatment is important.

NATURAL HISTORY

There is a lack of large-scale prospective natural history studies of genital warts. In the historic study by Oriel the average time to development of warts was three months, but could be over two years[3]. The factors associated with development of exophytic warts from latent and subclinical HPV are not known, but the immune response is undoubtedly important. For instance, in a longitudinal study the incidence of genital warts in HIV-positive women was 8.2 per 100 person years compared with 0.8 in those who were HIV-negative, despite similar levels of latent HPV infection[1]. Spontaneous regression of established lesions undoubtedly occurs. It has been reported in 10–30% of patients in the placebo arms of treatment trials. In a natural history cohort study of latent and subclinical HPV and genital warts, in men, the median time to cure of HPV was 15 months (range 12–21). Time to cure did not differ significantly in those treated versus those not treated, but the number of warts did decrease significantly in those treated and fewer new HPV lesions appeared[4]. At the cellular level spontaneous regression is accompanied by an active

cell-mediated response[5]. So a person's immune response most probably determines whether an HPV infection becomes clinically manifest, how favourably the warts respond to any treatment and whether they recur.

EFFECT OF TREATMENT

In her excellent review on genital warts, Stone highlighted the four areas of importance when assessing how effective treatment is of an STI[6]. These are elimination or reduction of symptoms, prevention of associated morbidity and long-term complications, eradication of infection and interruption of transmission. It is helpful to look at these areas in turn to see how effective our current treatment options are for genital warts.

Elimination or reduction of symptoms

Genital warts are usually asymptomatic and are often found incidentally. One study found that 30% of women learned they had genital warts during a visit for an unrelated problem[7]. They rarely cause any discomfort, the greatest physical discomfort is associated with treatment. Once the patient is aware of them the main symptom of genital warts is their cosmetic appearance and resultant psychological consequences.

Prevention of associated morbidity and long-term complications

Long-term medical complications from HPV-6 and 11 are rare. Very occasionally they can form Buschke–Löwenstein giant condyloma, a locally invasive, but non-metastasizing tumour[8]. Vertical transmission can occur, but in view of the high prevalence of HPV-6 and 11 in women of childbearing age and the infrequency of laryngeal and genital warts in infants, it is rare[9]. HPV-6 and 11 are not associated with cervical cancer as, unlike high-risk HPV types, they are unable to integrate into the host chromosome, and they do not produce proteins with transforming activity that interfere with cellular regulation. Women with genital warts frequently have subclinical HPV-6 and 11 infections, which may present as low-grade cervical abnormalities. Consequently, studies of women with genital warts have reported increased rates of cervical cytology abnormality[10] or CIN[11], but the abnormalities have been mainly low-grade lesions. Studies looking at cervical cancer have reported no significant increase in women with a history of genital warts[12]. Consequently, in the UK, the Cervical Screening Programme recommends normal interval screening for women with genital warts[13].

The main morbidity of genital warts is psychological. Visible warts can have a negative effect on body image and self-esteem. A number of studies have reported high levels of depression and diminished sexual function. In a survey of subscribers to a journal for people with HPV infection, more than two-thirds experienced depression, isolation and fear of rejection when they discovered they had HPV infection. There was also a psychosexual effect with more than two-thirds enjoying sex less, feeling less desirable and fearing rejection. More people reported a negative impact on sexual feelings and behaviour than physical discomfort caused by the HPV[14]. In a study of women being treated for genital warts, they reported less pleasantness and were less active and sociable than a control group of women without warts. About 15% abstained from sex, had a break up of their relationship, or developed negative feelings for their current partner[15]. The psychological impact of genital warts should therefore be addressed in addition to the medical treatment[16]. Accurate and consistent written and verbal information are important supplements to the medical management.

Eradication of infection

The ideal treatment outcome would be complete viral eradication, but this is not possible. Treatments focus on removal of exophytic warts, leaving the surrounding subclinical and latent HPV infection. Studies of the natural history of genital warts[4], and treatment trials with placebo arms have shown that treatment of warts significantly improves reduction and clearance of genital warts, but time to clearance of latent HPV infection is not affected[4]. However, effective treatment of warts does reduce HPV viral load[17]. So there is evidence that treatment reduces infection but does not completely eradicate it.

No single treatment is ideal for all patients or all warts. The size, anatomical location, number and morphology of warts may all influence treatment decisions. Treatment of genital warts is often painful, inconvenient — requiring multiple visits, expensive in staff time involved in treatment and time lost from work, and may produce poor clearance rates and frequent recurrences. Despite all the inadequacies, most patients will be wart-free within three months of starting treatment, but in a significant proportion the warts will recur. The treatment chosen should be no worse or more dangerous than the disease itself. As many patients require therapy over several weeks, the treatment should be tailored to the patients' disease and needs as well as to the available resources. Yet one study reported that 86% of patients had no, or little, involvement in the selection of treatment[7].

A number of guidelines and reviews have been produced indicating the varying clearance and recurrence rates for different types of treatments[18–21]. There are wide ranges in the figures, and most overlap so that it is impossible to tell if one treatment is better than another. It is often difficult for clinicians to make evidence-based choices of treatment because there have been very few comparative treatment trials for genital warts. In

randomized trials of podophyllin versus podophyllotoxin all have shown podophyllotoxin to give better initial clearance rates and lower recurrence rates, with significantly better overall clearance rates[22–24]. Podophyllotoxin also has the advantage of being a patient-applied treatment, and has been shown to be a more cost-effective therapy[25]. Cryotherapy[26,27], electrocautery[27], surgical[28] and scissor[29] excision, have all been shown to be superior to podophyllin in randomized trials. This universal inferiority of podophyllin calls into question its use in clinical practice, and some guidelines recommend it should not be used[19]. Systemic interferons and topical 5-fluorouracil are also not recommended for clinical use because of poor efficacy, expense and side effects, and lack of published trials respectively[19,20]. Cryotherapy has been found to be equivalent to trichloroacetic acid (TCA)[30,31] and electrocautery[27,32]. Imiquimod is a relatively new treatment for genital warts. It is a topical immune response modifier that activates cell-mediated immunity, so works by mimicking the mechanism of spontaneous regression[33]. Consequently it can be slower to take effect than ablative therapies. It is more effective in females with higher clearance rates reported than in circumcised men[34]. Recurrence rates have been lower than those published for other treatments, so overall clearance rates may be better, but there have been no direct comparative trials with other treatments. As a patient-applied therapy, this may also be a more cost effective treatment, but the only study assessing this used data from different treatment trials, not from a randomized trial[35]. It is not known if this immune modulating treatment clears subclinical and latent HPV infection.

There has been little published on combining treatments, yet this seems to be common in clinical practice[36]. One small study reported similar clearance and recurrence rates from TCA plus podophyllin, compared with TCA alone, but a significant benefit from the combined treatment in that fewer treatments were needed to achieve clearance[37]. It would be interesting to know if combining an ablative therapy, such as cryotherapy, with an immune response modulator, such as imiquimod, would give combined benefits of quicker time to wart clearance with fewer recurrences.

Some types of warts seem to respond to treatment better than others, but the published evidence supporting this is poor. Keratinization might be expected to impede topically applied therapy, but not ablative methods. Papular and keratinized warts tend to have poorer response rates with podophyllotoxin and podophyllin, as clearance rates on the penile shaft were lower than the preputial cavity[38]. Also clearance rates with imiquimod were lower in circumcised men[34] compared with uncircumcised[39]. The studies of TCA, cryotherapy, electrocautery or surgery have not differentiated cure rates with different wart types. Patients with larger numbers of warts at presentation may take longer to clear[40]. Although smoking has been found to be a risk factor for acquiring warts[41], there is no evidence that smoking during treatment affects the outcome of treatment[4,40]. Treatment algorithms may help improve clearance rates[42].

Treating the male sexual partner's HPV lesions does not improve wart clearance in women, nor prevent recurrences[43]. Subclinical HPV is multifocal and this finding suggests recurrences mainly come from subclinical HPV rather than re-infection.

Interruption of transmission

Genital warts are highly infectious. Approximately two-thirds of sexual partners will develop clinically apparent warts within nine months[3]. Studies looking for subclinical infection have found that up to 94% of partners have lesions[44]. So sexual partners may well already be infected when a patient presents for treatment. Sexual partners are more likely to be infected if the HPV viral load is higher and with longer relationships. In a study assessing viral load and infection within couples, the mean viral load was much higher in couples where both were infected than in those with only one partner infected[45]. Also, when both partners were infected one had a much higher viral load than the other. This suggests that the viral load needs to get to a certain level before it can be sexually transmitted. Infection of both partners was more likely with longer duration of the relationship, suggesting repeated exposure may be necessary for transmission.

When both partners are infected they do not necessarily have the same HPV types. In a study sampling multiple sites of the genital tract, samples from the same patient tended to have the same HPV types, but sexual partners did not consistently have HPV types in common[46]. This suggests that some have been infected from a previous partner, which is not surprising, as HPV DNA carriage on the genital tract is thought to be present in 15–25% of young people, with levels as high as 46% being found in sexually-active female students[47].

Although there are no studies assessing whether exophytic warts are more infectious than subclinical lesions, HPV viral load increases from latent to subclinical to clinical infection. Biological plausibility therefore suggests that warts are more infectious than subclinical infection. So as successful treatment of warts does reduce HPV viral load[17] it may reduce transmission. However successful removal of warts still leaves subclinical or latent infection and these remain as areas of possible transmission.

We do not know how to prevent HPV transmission completely. There have been a number of conflicting studies about the relationship between condom use and HPV infection. Some studies looking at risk factors for genital HPV infection found that condom use was not protective[48–50].

Presumably for condoms to offer any protection against the spread of HPV they need to be used consistently, but not all of these studies defined the level of condom use. However, some have stratified the level of condom use, and still found no protection against acquiring genital warts from consistent use[50]. Several other studies have suggested that consistent condom use can reduce the risk of acquiring genital warts or HPV infection. In a study of risk factors for genital HPV infection in males, failure to use a condom was statistically associated with HPV infection, and regular condom use was protective of infection[51]. In a cohort study regular condom use significantly protected initially healthy men from acquiring HPV lesions[4]. A case-controlled study for acquisition of genital warts stratified condom use into never, sometimes (less than 50% use), usually (more than 50% use) and always except breakages. Even after adjusting for other known risk factors, condom use remained significant. Consistent condom use significantly protected against acquiring genital warts (odds ratio [OR] 0.7), and never using condoms significantly increased the risk by 1.9[52]. A study of HPV infection detected by polymerase chain reaction (PCR) and hybridization in female sex workers found failure to use condoms to be significantly associated with HPV infection. Regular use of condoms for over six years significantly protected against HPV infection (OR 0.4)[53].

There are no published studies showing that condom use reduces transmission of HPV from people with genital warts. By the time warts have developed and been detected, it is likely that the partner has already been infected, so there may be no benefit from introducing condom use into an established relationship. However, if the sexual partner is uninfected using a condom may protect against HPV lesions and genital warts. Condom use should be encouraged in new relationships.

CONCLUSIONS

When managing this very common condition, the clinician should be mindful that current treatments are not very successful and recurrences are common. The therapy can be worse than the disease, entailing multiple visits and painful treatment. Patients should therefore be allowed to make informed choices about their treatment. Genital warts cause few symptoms and pose little long-term risk. Removal of warts may not reduce transmission; subclinical infection will persist and may be a source of transmission and recurrence. If the sexual partner is uninfected using a condom may protect against HPV lesions and genital warts, but it is likely that many sexual partners will already be infected.

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Based on: Wilson J. Treatment of genital warts — what's the evidence? *Int J STD AIDS* 2002; **13**: 216–220

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For each of the following statements, circle whether it is True or False:

1. Genital warts:
   (a) Are the most common sexually transmitted infection in Europe. TRUE/FALSE
   (b) Have a prevalence of about 10% in the general population. TRUE/FALSE
   (c) Have an incubation period of about 1 week. TRUE/FALSE
   (d) Are always symptomatic. TRUE/FALSE
   (e) Have few long-term medical complications. TRUE/FALSE
2. Women with genital warts:
   (a) Are at higher risk of cervical cancer. TRUE/FALSE
   (b) Are recommended to have more frequent cervical cytology screening in the UK. TRUE/FALSE
   (c) Are more likely to have psychosexual problems than women without warts. TRUE/FALSE
   (d) When pregnant, have a high risk of vertical transmission with vaginal delivery. TRUE/FALSE
   (e) Have improved clearance rates if their sexual partners are also treated. TRUE/FALSE
3. Latent human papillomavirus infection:
   (a) Is not infectious to sexual partners. TRUE/FALSE
   (b) Can be detected with the naked eye. TRUE/FALSE
   (c) Usually takes 5 years to clear. TRUE/FALSE
   (d) Has been found in more than 30% of young sexually-active females. TRUE/FALSE
   (e) Is cleared more quickly by treating with cryotherapy. TRUE/FALSE
4. In the treatment of genital warts:
   (a) Warts on the penile shaft are easier to clear than at other anatomical sites. TRUE/FALSE
   (b) Topical 5-fluorouracil has a high safety profile. TRUE/FALSE
   (c) Combined treatments give proven better clearance rates. TRUE/FALSE
   (d) Clearance rates are better in non-smokers than smokers. TRUE/FALSE
   (e) Podophyllin has inferior clearance rates to most other treatments. TRUE/FALSE
5. Transmission of genital warts:
   (a) Is higher if the HPV viral load is higher. TRUE/FALSE
   (b) Is higher with longer sexual relationships. TRUE/FALSE
   (c) Can be prevented by patients with warts using condoms. TRUE/FALSE
   (d) To sexual partners is low, with few becoming infected. TRUE/FALSE
   (e) Acquisition of genital warts can be protected against by consistent condom use. TRUE/FALSE
6. Treatment of genital warts:
   (a) Eradicates all HPV infection. TRUE/FALSE
   (b) Reduces HPV viral load. TRUE/FALSE
   (c) Gives high sustained clearance rates. TRUE/FALSE
   (d) Frequently requires multiple treatment episodes. TRUE/FALSE
   (e) Results in the majority of patients being wart free within 3 months. TRUE/FALSE
7. In the treatment of genital warts:
   (a) Cryotherapy should be first-line treatment for all patients. TRUE/FALSE
   (b) Patients with larger number of warts at presentation may take longer to clear. TRUE/FALSE
   (c) Clinical algorithms can improve clearance rates. TRUE/FALSE
   (d) Podophyllotoxin and imiquimod can be used as patient-applied therapies. TRUE/FALSE
   (e) Women have better clearance rates than men with imiquimod. TRUE/FALSE
8. Cell mediated immunity:
   (a) Is stimulated by systemic interferon, resulting in the best clearance rates of all treatments. TRUE/FALSE
   (b) Can be stimulated by the topical application of imiquimod. TRUE/FALSE
   (c) An active response is seen in spontaneously regressing warts. TRUE/FALSE
   (d) Determines whether latent HPV infection develops into clinical disease. TRUE/FALSE
   (e) May be important in disease recurrence. TRUE/FALSE

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