

Genital Papillomavirus Infection (GPVI) – Clinical Guidelines from the Swedish Section of Venereology

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Background

Human papillomavirus (HPV) is an epidermotropic virus that can cause varying grades of epidermal hyperplasia and/or dysplasia. Approximately 200 types of HPV have been characterized, of which approximately 30 have tropism for the genital epithelium. HPV 6 and 11 are the most common benign “low-risk” HPV types, and are found in genital and anal warts. HPV 16 and 18 are the most common oncogenic “high-risk” types, and are found mostly in dysplastic lesions (“intraepithelial neoplasia”).

Genital HPV infection is mainly a sexually transmitted disease. During recent years other possible means of transmission have been discussed, such as via digital contact, towels and underwear. However, the relevance of these kinds of transmission is unclear; the virus is very sensitive to a dry environment and probably cannot survive outside the human body for a long time. Autoinoculation via the fingers might also occur from genital warts to other genital areas.

There have been very few studies of the incubation period of HPV. In general the incubation period is long; typically up to 2–6 months for visible warts, but it can also be much longer. Visible warts are found in 0.5–1% of adults, but subclinical (flat) lesions are certainly much more common. Asymptomatic infection (the presence of HPV DNA on the genital mucosa) is present in 20–30% of sexually active people in the age range 20–30 years, i.e. it is as common as genital herpes.

Genital warts can be sub-divided morphologically into acuminated, papulous and flat lesions. The colour of the warts varies depending on the localization and age of the lesions. An uncommon type of lesion caused by high-risk HPV is bowenoid papulosis, which usually affects young people. These lesions are multiple, often red-brown and papulous, but might also be flat.

HPV requires (like herpes simplex virus; HSV) a fissure for entrance into the mucosa, and warts are usually found on areas where such fissures occur during sexual intercourse. Intimate shaving of the pubic area also causes fissures in the skin. Common locations among men are the inner aspect of the foreskin, the frenulum and the glans penis. Warts might also be located

on the penile shaft (a common location among circumcised men). In women, the medial part of the vulva, the posterior commissure, around the clitoris and the introitus, are common locations for lesions. Warts might also be present in the vagina and on the portio. These locations are predilection sites for cervical intraepithelial neoplasia (CIN) and cancer (but these entities require infection with a high-risk type). Warts in the meatus are more common in men than in women. Both sexes might have perianal warts. Intra-anal warts, on the other hand, seem to require receptive anal intercourse. Often latent virus is found on surrounding genital skin and mucosa.

Genital warts in children

Discussion about contagiousness is an issue of concern when dealing with anogenital warts in children. Infections via the birth canal and by social contacts are probably the most common ways for children to become affected. The possibility of sexual abuse should always be considered. The suspicion of sexual abuse is generally thought to be less for children under 3 years of age. Very few reliable criteria exist for such investigations, and generally multidisciplinary teams are recommended when dealing with these patients. Among children, cutaneous HPV types are sometimes found in genital lesions; a fact that does not exclude the possibility of sexual abuse.

Diagnosis

“Genital warts” is mainly a clinical diagnosis. In atypical cases, or for diagnosis of grade of dysplasia, biopsy can be considered. Typical histopathological changes include epidermal hyperplasia, acanthosis, hyper- and parakeratosis, koilocytosis (virus-degenerated epithelial cells with a hyperchromatic nucleus and perinuclear vacuolization) and, in some cases, varying degrees of intraepithelial neoplasia. It is not possible to culture HPV, but it can be diagnosed by HPV DNA hybridization techniques (usually polymerase chain reaction; PCR).

Treatment

Available treatment methods mainly cause the elimination of visible warts. Latent virus might still be present and may cause recurrences. Treatment therefore often has to be repeated.

Approximately 20% of patients experience recurrences, and represent a therapeutic problem group, while 80% get rid of their warts within a year. The choice of treatment method has to be individualized. The effects of the drugs vary and patients tolerate the side-effects differently. In some cases, expectation of spontaneous regression might be an alternative method. Combinations of different methods of treatment are sometimes used. If warts have been absent for 3–6 months recurrences are uncommon, although transmission by latent infection cannot be fully excluded. In general, an immune response for the respective HPV type develops. Reactivation of an earlier infection might, in some cases, occur after many years, but infection with a new HPV type is more probable.

Indications for treatment

The goal of treatment is to eradicate visible and symptomatic lesions (psychosexual problems, pain, itching, dyspareunia). Dysplastic lesions are generally treated. It is important to provide psychological support for the patients.

Chemical home-treatment

Podophyllotoxin (solution or cream). The drug is applied twice a day for 3 days. Treatment can be repeated after 4–7 days; 1–4 treatment sessions are recommended. This form of therapy is usually best for acuminate warts on the genital mucosa, but is less effective on thicker epithelium, in the meatus and in the perianal area.

To avoid extensive local side-effects (ulcers, pain, tenderness), patients should be instructed carefully in application of this therapy.

Imiquimod cream. This drug has an interesting mode of action, and works by induction of cytokines important for HPV elimination. The cream is applied 3 times per week for up to 16 weeks. Local side-effects do occur. In contrast to podophyllotoxin, influenza-like symptoms have also been described. This drug is more expensive, but is a good alternative in selected cases. For genital warts, a better effect in women than

in men has been reported. Imiquimod is often used as a first alternative for perianal warts. Case reports for treatment of genital dysplastic lesions also exist.

Surgical treatment

Surgical treatment can be through diathermy, carbon dioxide (CO₂) laser, cryotherapy or excision. The choice of these destructive surgical treatment methods depends on tradition and skill.

Pregnant women

Podophyllotoxin is contra-indicated during pregnancy. Imiquimod should also be avoided. Pregnant women are usually treated by surgery, but sometimes expectation of spontaneous regression is recommended. Infection through the birth canal might occur, in rare cases causing juvenile laryngeal papillomas.

Partner aspects

Examination of the partner is not mandatory. The partner is recommended to attend a clinic if they are experiencing any problems. Condom use is not necessary in a steady relationship.

Vaccines

Two vaccines currently exist: Gardasil® (quadrivalent: HPV 6, 11, 16, 18) and Cervarix® (bivalent: HPV 16 and 18). The vaccines are prophylactic and should be given before an individual becomes sexually active. However, vaccination for already sexually active individuals is also recommended in many cases. The vaccines consist of synthetically produced virus-like particles and have been shown to be very effective. An efficacy of almost 100% has been reported for the included HPV types in immunologically naive individuals. Mainly women have been studied, but a few male studies exist; Gardasil® is also registered for use in men. General vaccination in young women has been implemented in many countries. Studies of vaccines for multiple HPV types are on-going, and these new vaccines may become commercially available in the future.