Anogenital Warts

Synonyms: human papillomavirus (HPV), condylomata acuminata, condyloma acuminata, genital warts, penile warts, vulval warts, labial warts, anogenital warts, vaginal warts, cervical warts

Anogenital warts are benign proliferative epithelial growths caused by infection with human papillomavirus (HPV). They are very common, particularly in young people. However, it is hoped incidence will decline significantly as a result of widespread HPV vaccination. All those with anogenital warts should be referred to specialist sexual health clinics for assessment and treatment.

Aetiology

- Anogenital warts are caused by infection with HPV. There are >100 of these double-stranded-DNA papovaviruses characterised, with most now fully DNA-sequenced.
- HPV is transmitted sexually in most cases but can also be transmitted prenatally, by auto-inoculation or hetero-inoculation from non-genital warts.
- Anogenital warts have a 60% transmission rate between partners.
- Over 95% of genital warts are caused by infection with HPV types 6 and 11. These types are not associated with a significant risk of neoplastic transformation.
- Types 16 and 18 are associated with a high risk of neoplastic transformation. There may be co-infection with these high-risk types of HPV.

Risk factors

- Smoking.
- Multiple sexual partners.
- Early age of onset of sexual intercourse.
- History of other sexually transmitted infections (STIs). (Up to 20% of those with anogenital warts have other STIs.)
- Anoreceptive intercourse. However, perianal warts can occur in the absence of anal intercourse. Perianal warts occur in men and women but are more common in men who have sex with men.\[6\] Warts within the anal canal are usually, but not always, associated with penetrative anal intercourse.\[1\]
- Manual sexual practices such as fisting and fingering may increase the risk of anal warts.\[6\]
- Immunosuppression (including iatrogenic variety in transplant recipients and HIV).\[7\]

Epidemiology

Genital warts are the most commonly diagnosed viral STI in the UK. One study in England, based on data from general practice and genitourinary medicine clinics reported 90,531 new and 68,259 recurrent cases in the year 2008.\[8\] HPV prevalence prior to widespread vaccination, which began in 2008, was shown to be around 35% in sexually active 14- to 24-year-olds undergoing chlamydia screening.\[8\]

However, since introduction of a national HPV vaccination programme in the UK, incidence is expected to drop significantly. This has been demonstrated in countries such as Australia, which was the first country to introduce a national vaccination programme with the quadrivalent vaccine. Results after five years from sexual health clinics showed a marked reduction of genital warts in women and also in heterosexual men in the vaccinated age group.\[10\] Between 2007 and 2011, the percentage of women having genital warts in sexual health clinics in the relevant age group dropped from 11.5% to 0.85%. In 2011 no diagnoses of genital warts were made in girls who had been vaccinated. The UK can expect similar reduction but results will be delayed, as the bivalent vaccine was used until 2012. There is already evidence of some decline in the incidence of genital warts attributable to the bivalent vaccine.\[11\]
Presentation

Symptoms\textsuperscript{[1, 2]}

Usually the presentation is with the presence of a lesion or lesions, which are usually painless. Lesions may be disfiguring or embarrassing. They may cause itching, bleeding or dyspareunia. Urethral lesions may cause distortion of the urinary stream.

By SOA-AIDS Amsterdam via Wikimedia Commons

A relevant sexual history should be obtained to assess the risk of other STIs and sexual health needs:\textsuperscript{[5]}

- Other symptoms - eg, urethral/vaginal discharge, pelvic or scrotal pain, intermenstrual or postcoital bleeding, dyspareunia.
- Sexual activity in the preceding three months.
- Contraceptive and condom use.
- Possibility of pregnancy.
- HIV risk activities.

Signs\textsuperscript{[1, 2]}

- Lesions may be single but are often multiple. A number of lesions may form a confluent mass. They may become huge in immunocompromised patients.
- Warts on moist, non-hairy skin are usually soft and non-keratinised, whereas those on dry hairy skin are more likely to be firm and keratinised.
- Warts may be broad-based or pedunculated.
- Warts may be pigmented or not. Colour varies and may be pink, red, white, grey or brown.
- They are often found on areas subject to trauma during sexual intercourse.
- Sites where lesions are found include:
  - In uncircumcised males: frenulum, corona, glans penis inner foreskin, as well as the urethral meatus, penile shaft and scrotum.
  - In circumcised males: mainly the penile shaft, also the urethral meatus and scrotum.
  - In females: labia, clitoris, urethral meatus, introitus, vagina and cervix.
  - Both sexes: perineum, groin, pubis, perineum, perianal area and anal canal.

The anogenital and surrounding skin should be examined under good illumination. Female patients should undergo a vaginal speculum examination, and proctoscopy may be indicated in both sexes if there is a history of anoreceptive sex. Recording lesions on genital maps can be useful to enable a visual record and monitor response to treatment.
Investigation\textsuperscript{[2]}

Diagnosis by biopsy and viral typing is not routinely required and tends to be reserved for where diagnosis is uncertain or for recalcitrant warts, warts with atypical features or where there is high risk of HPV-related malignancy.

Be suspicious of unusual presentations (eg, flat or only slightly raised lesions, pigmented, indurated or ulcerated warts), particularly in patients aged over 35 years or with other risk factors. Also be aware of the development of new symptoms (eg, itching, pain, crustng, bleeding) and warts that are unresponsive to treatment. Arrange for biopsy to exclude malignancy in these situations.

An appropriate screen for other STIs should be carried out.

Differential diagnosis\textsuperscript{[5, 12]}

- Molluscum contagiosum.
- Epidermoid cysts.
- Hair follicles.
- Sebaceous glands.
- Skin tags.
- Pearly penile papules (normal variant: 1-3 rows of smooth, discrete, non-coalescing, 1-2 mm papules appearing on the margin of the glans).\textsuperscript{[13]}
- Vulval papillomatosis (normal variant: regularly shaped, non-coalescing, largely symmetrical papillae on the inside of the labia minora and vestibule).\textsuperscript{[14]}
- Hymen remnants.
- Intra-epithelial neoplasia (vulval, anal or penile).
- Malignancy.
- Condyloma lata (secondary syphilis).

Associated diseases

Up to 20\% of those with anogenital warts will have another STI.\textsuperscript{[5]}

The majority of external genital warts are caused by HPV types 6 and 11 which are not associated with significantly increased risk of neoplastic transformation. However, a minority of genital warts are caused by HPV types 16 and 18 and there is also a significant risk of co-infection with these types. These oncogenic types are associated with an increased risk of:\textsuperscript{[15]}

- Cervical cancer.
- Vaginal cancer, vulval cancer and penile cancer.
- Anal cancers.
- Oral and oropharyngeal cancers.

Management\textsuperscript{[1, 2, 5]}

General points

- Patients will require a detailed explanation of the condition with emphasis on long-term health implications for themselves and their partners. Reinforce with written information. Explain the long latent period associated with HPV and that recurrence of warts in one partner does not imply infidelity.
- Data are conflicting regarding condom use. Condoms are known to protect against transmission of anogenital warts but may not protect against transmission of HPV. Condom use is advised until resolution of lesions has occurred.
- Individuals should be aware that the HPV persists after clinical clearance of warts for very variable lengths of time.
- Psychological distress is common - referral for counselling may be appropriate.
- 20\% or more of patients with genital warts have concurrent STIs, so appropriate screening should be discussed and offered (including chlamydia, gonorrhoea, HIV, syphilis and hepatitis B and C).
- Current partners and if possible partners in the previous six months should be assessed and educated with regard to prevention of STIs.
- Advice about smoking cessation should be given. There is evidence that non-smokers have a better response than smokers to treatment.

Referral

Ideally anyone with anogenital warts should be referred to a sexual health clinic. This is because in the specialist setting:

- There is more accurate testing for other STIs and there are better facilities for treating and contact tracing where associated infections are found.
- There is better diagnostic accuracy.
- A full range of treatment options is available, including surgical ablation.
- Consistent information is available.
- There is additional confidentiality.

Referral is particularly important where:
The diagnosis is unclear. There is suspicion of intraepithelial neoplasia or malignancy (urgent referral). There are internal warts in difficult-to-reach sites (intravaginal, cervical, urethral meatus or intra-anal). The patient is a child, pregnant or immunosuppressed. There is treatment failure or where treatment cannot be tolerated due to side-effects. There are problematic recurrences. There are positive results from the screen for other STIs.

Treatment options
- No treatment. One third of warts regress spontaneously within six months.
- Podophyllotoxin self-application is suitable for soft, non-keratinised external genital warts. 0.15% cream or 0.5% solution should be used twice-daily for three days, followed by four rest days. If the wart persists, treatment may be repeated at weekly intervals, for a total of five weeks. The solution is more convenient for penile warts whereas the cream is more useful for vulval and anal lesions.
- Imiquimod 5% cream self-application can be used for keratinised lesions and non-keratinised external lesions. It should be applied thinly three times a week at night until the lesions resolve, for a maximum of 16 weeks.
- Trichloracetic acid is less used due to its corrosive action on skin but is occasionally employed by hospital specialists for warts that are very indurated or in pregnant patients in whom other agents are contra-indicated. This is applied by the specialist rather than for self application.
- An ointment containing a mixture of green tea catechins marketed as Veregen® is used in the USA, Austria and Germany but is not currently licensed in the UK [18].
- Ablation. Cryotherapy, excision, electrocautery or laser can be used.

Efficacy of treatment
- Only surgical treatments have clearance rates approaching 100%.
- Recurrences occur after all therapies.
- The recurrence rate for new lesions occurring in previously treated or new areas is often in the region of 20-30%.
- All treatments are associated with itching, pain, burning and erosions.
- All topical treatments can cause local skin reactions and, where severe, patients must stop treatment and seek advice. Normal surrounding skin may be protected from podophyllotoxin by the use of petroleum jelly. Avoid contact with broken skin and open wounds. Unprotected sexual contact soon after application should be avoided (as it may have an irritant effect on the partner). Condoms may be weakened if in contact with imiquimod.
- Podophyllotoxin treatment is associated with a 43-83% clearance rate and up to 65% have adverse effects.
- Imiquimod treatment has a 35-68% clearance rate.
- Follow-up is required to assess response and side-effects and to check for new lesions. Continue treatment if response is good but new lesions are developing. Change treatment if it is not tolerated or response to treatment by six weeks (8-12 weeks for imiquimod) is poor.
**Specific treatment situations**
- Cervical warts: should be treated by a gynaecologist and require colposcopy.\(^1\)
- Intra-anal warts: require proctoscopy and possibly surgical referral.
- Pregnancy: avoid podophyllotoxin and imiquimod in pregnancy. Cryotherapy is often used to try to minimise lesions present at delivery but risks (perinatal transmission of genital warts, laryngeal papillomatosis, obstructed labour) to the baby are usually considered small and not an indication for caesarean section.

**Genital warts in children**
The discovery of external genital warts in children often raises concern about sexual abuse.\(^{17}\) National Institute for Health and Care Excellence (NICE) guidance recommends considering sexual abuse in a child younger than 13 years with anogenital warts unless there is clear evidence of:\(^{18}\)
- Mother-to-child transmission during birth (it is **not** currently known at what age this can be confidently excluded).
- Non-sexual transmission from a household member.

Studies suggest sexual transmission as the cause of infection in between 31-58% of children with anogenital warts. One study found an increase in HPV infection in children who had been abused.\(^{19}\) However, it is often very difficult to determine the mode of transmission in children, even with viral typing of the index case and contacts, and the presence of warts or HPV infection without supporting social and clinical evidence cannot be taken as diagnostic of sexual abuse.\(^{20}\) Advice should be sought from experienced child protection colleagues.

There is a lack of controlled trials comparing treatments of anogenital warts in children and adolescents.\(^{17}\)

**Prognosis**\(^4\)
Explain to patients that untreated external genital warts may:
- Resolve spontaneously - up to one third spontaneously regress within six months.
- Remain the same.
- Increase in size.

Lifelong subclinical infection may persist. Recurrences are common.

Complications include psychological distress, malignant change within existing warts and an increased risk of certain cancers.

Over 95% of genital warts are caused by HPV types which are low-risk for neoplastic transformation. However, there may be co-infection with oncogenic HPV types. The risk of cervical cancer in situ has been shown to be doubled in women with a history of anogenital warts.\(^{21}\) People with anogenital warts have been shown to have an increased risk of anogenital cancers (anal, vaginal, vulval and cervical), head and neck cancers, non-melanoma skin cancers, smoking-related cancers (bladder, lung, liver) and lymphomas.\(^{22}\)

Nationally, the annual cost of treatment of genital warts is enormous (an estimated £16.8 million in England in 2008) and it is hoped vaccination will significantly reduce this.\(^8\)

**Prevention**

**Condoms**
Data are conflicting but there is evidence of some protection against anogenital warts, although less convincingly for HPV itself.\(^{1, 23}\)
Vaccination

There are two HPV vaccines available in the UK: Cervarix® and Gardasil®.

- Cervarix® is a bivalent vaccine, meaning it protects against two strains of HPV. Cervarix® protects against HPV16 and HPV18 and so is aimed to reduce (in time) the number of cases of cervical cancer. When the UK first started immunising young women against HPV, this was the vaccine chosen.

- Gardasil® is a quadrivalent vaccine, meaning it protects against four strains of HPV. Gardasil® protects against HPV16, HPV18 and HPV6 and HPV11. This means that it also protects against genital warts as well as cervical cancer.

In September 2012 the UK HPV vaccination programme switched to using Gardasil®.

HPV vaccines are highly effective at preventing the infection of susceptible women with the HPV types covered by the vaccine. In clinical trials, both vaccines are over 99% effective at preventing pre-cancerous lesions associated with HPV types 16 or 18 in young women. Current studies suggest that protection is maintained for at least ten years. Based on the immune responses, it is expected that protection will be extended further; long-term follow-up studies are in place.

Males are not currently covered by the national immunisation programme. This is currently the subject of much debate and controversy. Gender-neutral vaccination has been recommended in other countries, such as the USA, Canada, Australia and Austria. This is because, although there may be a herd immunity effect in reducing genital warts in heterosexual men, it discriminates against men who have sex with men.

Further reading & references

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