



HPV

AUSTRALIA AND NEW ZEALAND
HPV PROJECT

Australia and New Zealand HPV Project

Guidelines for the Management of Genital HPV in Australia and New Zealand

5th Edition - 2007

1st Edition 1999

2nd Edition 2001

3rd Edition 2002

4th Edition 2004

Produced by the Professional Advisory Board (PAB)
of the Australia and New Zealand HPV Project

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For a list of the Professional Advisory Board (PAB) members,
refer to page 34.

ABOUT THIS DOCUMENT

This document is a consensus opinion of the Professional Advisory Board (PAB) of the Australia and New Zealand HPV Project. The PAB has representation from patients and medical and nursing bodies involved in the management of people with genital HPV and/or genital warts. A process was undertaken to evaluate contemporary international literature and develop best practice regarding the diagnosis, treatment and evaluation of patients with HPV infection/genital warts and their sex partners, in Australasia. The recommendations are based on strong evidence in the literature or reasonable suppositions and opinions of experts. The PAB works on a voluntary basis.

Commonwealth Serum Laboratories [CSL] provided an educational grant towards the publication of these guidelines, they did not participate in their development.

The guidelines' recommendations have been rated under the following evidence-based categories:

- GRADE A:** Very strong evidence.
One or more properly randomised controlled clinical trials.
- GRADE B:** Fairly strong evidence.
One or more well designed observational studies (i.e. non-randomised clinical trial cohort, case control or time series study; or non-controlled experimental trials).
- GRADE C:** Weak evidence or firmly held opinion.
Opinions of respected authorities that were based on clinical experience, descriptive studies, and/or reports of expert committees.

TABLE OF CONTENTS

	Page
Introduction	1
Epidemiology of Genital HPV Infection	2
Transmission of Genital HPV Infection	4
HPV and Cancer	5
HPV Vaccines	6
Clinical Presentation and Diagnosis	8
Molecular (DNA) Diagnosis of Genital HPV Infection	9
Treatment of Genital HPV Infection and Genital Warts	11
Table 1: Treatment by site	18
Table 2: Summary of treatment options.	18
Table 3: Factors that may influence the selection of treatment for warts	20
Special Situations.	21
Key Issues in Counselling.	23
Key Information for Patients	24
Guidelines on the Management of HPV in Childhood	25
Clinical Presentations of Genital HPV.	30
References.	31
Professional Advisory Board	34

HUMAN PAPILOMAVIRUS (HPV) AND ANOGENITAL CANCER

Introduction

Previous editions of these Guidelines have focused largely on the management of genital warts. In these Guidelines there has been a change of emphasis.

During the 1970s emerging evidence indicated that the wart virus may be central in the pathogenesis of cervical dysplasia and cancer. Since that time developments in the field of molecular medicine together with many large epidemiological studies have providing provided convincing evidence of the causal role of HPV in cervical cancer.

More recently, HPV vaccines have been developed and subjected to extensive field trials. These have demonstrated the safety, efficacy in preventing infection and disease in the HPV types contained within the vaccine. Our challenge now is to translate the laboratory knowledge and results of the field trials into a practical reality for New Zealand women.

R W Jones

Chairman

EPIDEMIOLOGY OF GENITAL HPV INFECTION

Incidence and prevalence

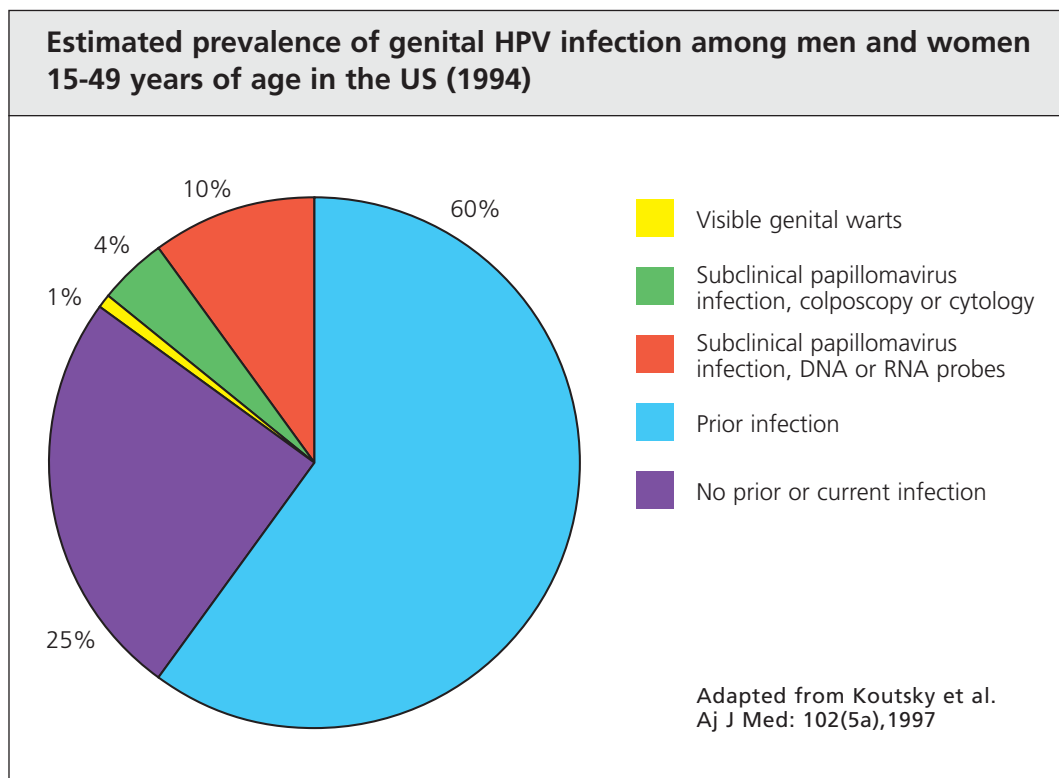
HPV infection is ubiquitous with approximately 75% of women being exposed to at least one HPV infection in their lifetime¹. A recent meta analysis estimated HPV prevalence among women with normal cervical cytology using data from 78 published studies.¹ The highest prevalence is in young women (20-25% around age 20) falling to 10% at age 30 and falling slightly thereafter.¹ A small increase in women over 65 years may reflect reactivation of previously undetectable infection acquired earlier in life, new infections, or a cohort effect.² HPV prevalence in men is lower than women as penile epithelium may be less receptive to High Risk (HR) HPV types.³

Rates of HPV infection in young women are high following sexual debut and remain high with acquisition of each new partner.^{4,5} Sexual studies have reported cumulative incidences of 40% or more after three years of follow-up.² Evidence suggests the incidence of HPV infection is similarly high in men.³

HPV types 6 and 11 have been reported in 70% to 100% of visible genital warts. However co-infection with other HPV types is also common.⁶⁻¹⁰

Visible genital warts have a reported prevalence of 1% in the United States.^{8,11} In an Australian study on young woman aged 18 to 23 years, the lifetime self-reported incidence of genital warts was 3.1%.¹² Using members from the Dunedin Multidisciplinary Health and Development Study, Dickson et al determined the self-reported cumulative incidence of genital warts. In this cohort aged 21, men reported an incidence of 4.7% and women 6.9%.¹³ At age 32, men reported an incidence of 10.2% and women 12.2%¹⁴ (personal communication).

Most HPV infection is associated with initiation of sexual activity and thought to be transient although in some cases HPV infection remains latent and may reactivate years later.¹⁵



Risk factors associated with HPV acquisition

KEY POINTS

- **Genital HPV infection is common in people who have recently become sexually active.**
- **Most genital HPV infections are subclinical.**
- **On average 75% of sexually active adults will have had some form of HPV infection.**
- **Increasing number of sexual contacts is associated with increased risk of genital warts.**
- **For most people HPV infection is transient and clears spontaneously within 12 months but in some cases HPV infection remains latent and may reactivate years or decades later.**

Sexual activity

HPV infection is, in most cases, a sexually transmitted disease and in both men and women risk acquisition is influenced by sexual behavior.

A population-based case-control study on men showed having increasing numbers of partners in the previous five years was strongly associated with incident and recurrent condyloma acuminata.¹⁶ There was some increased risk with a history of any sexually transmitted infection. A similar study on women also showed a strong association with multiple partners.¹⁰ Women with five or more partners in the previous five years had a relative risk of 7.1 for incident warts and 12.8 for recurrent warts compared to those who had one partner over this time period.⁵ Winer et al showed that in female university students a report of a new partner was predictive of incident infection as measured by DNA positivity.⁵ In the large WAVE III study involving women aged 18 to 25, having more than three lifetime partners was independently associated with HPV infection.¹⁷

Contraceptive use

Although there has been conflicting evidence that oral contraceptive use increases the risk of genital warts,^{10,18} a study of 603 female university students demonstrated that use was predictive of cervical HPV DNA positivity.⁵

Smoking

The role of smoking in the risk of genital warts is unclear.^{10,18} This is in contrast to studies on cervical HPV infection as measured by HPV DNA which do show an association with cigarette smoking.^{5,19,20}

Pregnancy

There has been variable reporting on HPV rates in pregnant versus non-pregnant women.¹¹ It is thought that this may be due to higher levels of virus being found in pregnancy and thus detection methods which are more dependent on viral loads would find higher rates in pregnancy.

Role of immunity

Increased rates of HPV infection have been found in those with HIV. A case-control study compared renal transplant patients who were immunosuppressed with controls and found an increase in genital HPV.²¹

Condom use

See section on transmission.

TRANSMISSION OF GENITAL HPV INFECTION

KEY POINTS

- **HPV is highly infectious.**
- **If one member of a stable partnership has genital HPV infection, the other will be either infected or immune to that infection.**
- **Condoms do provide some limited protection against genital wart acquisition and CIN II and CIN III.**

Direct skin-to-skin contact spreads HPV infection most efficiently. The virus is not transmitted via blood or body fluid, e.g. semen. Genital forms of the virus target the mucous membranes and adjacent genital skin. One early study demonstrated that 60% of sexual partners of those with genital warts subsequently developed them as well.²² Using computer modelling, Barnabas et al estimated the per partner male to female transmission to be 60%.²³ Transmission is common for a number of reasons. Firstly, subclinical infections are common and asymptomatic. Secondly, warty lesions often go unnoticed, particularly in areas that are not easily inspected for the presence of warts.

Sexual contact is the most common form of transmission among adults. Vertical transmission and autoinoculation may occur rarely. It is also possible, but very uncommon, to transmit genital HPV infection to the mouth through oral sex. The mouth appears to be a less hospitable environment for genital strains of HPV than the genital area. Fomite transmission remains controversial.

For management of HPV infection in children, see page 25.

The latency period of genital HPV infection is extremely variable. Often, warts will appear after three to six months, but latency periods of many months or even decades have been reported.²⁴ Evidence for such extended latency periods is seen in immunocompromised and normal patients who, despite having been sexually inactive for many years, can suddenly develop warts or cervical abnormalities. It is important to emphasise that developing genital warts during a long-term relationship does not necessarily imply infidelity.

It is generally believed, although not proven, that clinically visible warts offer the greatest possibility for transmission, and that treating warts decreases that possibility. As it is difficult to detect HPV in its latent stage, it is impossible to know whether in some cases the immune system can completely clear the virus from the body, or whether the virus remains latent at undetectable levels, capable of re-emerging if the immune system weakens.

Manhart et al reviewed the effectiveness of condoms in prevention of HPV disease analysing 27 studies and concluded that there was no consistent evidence that condom use reduced the risk of becoming HPV DNA positive.²⁵ Condom use did however provide some protection against genital warts, although precise estimates were not available because of data inconsistency. Interestingly there was also some protection against cervical intraepithelial neoplasia (CIN) II and CIN III. The authors postulated that although condoms might not alter the rate of HPV infection (as measured by DNA analysis), the amount of virus may be decreased with consequent change in probability of disease expression. More recently however, a study with 82 female university students did show a significant decrease in genital HPV infection as measured by HPV DNA when condoms were used all the time, as compared to use 5% of the time.²⁶ For couples in long-term monogamous relationships, the value of condoms is debatable.

HPV AND CANCER

The infectious cycle of the human papilloma virus begins when infectious particles breach the epithelium of the lower ano-genital tract and enter basal epithelial cells. Daughter cells of the basal stem cells divide and mature vertically through the epithelium without further division. The virus replicates in suprabasal/squamous cells and mature virus is released into the environment when the superficial cells disintegrate. The E6 and E7 viral proteins are critical in the viral replication process and differences between these proteins in the high and low risk HPV types determine interactions with cell cycle proteins (pRb and p53), which in turn determine cellular proliferation or malignant transformation.²⁷

From the 1970s, epidemiological studies have provided increasing evidence to suggest a sexually transmitted factor was the aetiological agent in cervical cancer.²⁸ In 1995, the International Agency for Research in Cancer (IARC) stated that HPV 16 and 18 are carcinogenic, with limited evidence of the carcinogenicity of HPV 31 and 35.²⁹ Since then, the IARC has demonstrated HPV DNA in 99.7% of approximately 1,000 cervical cancers from 22 countries.^{30,31} In addition, many vulval, vaginal, anal and penile cancers are HPV related.³² HPV 16 and 18 account for about 70% of all cervical cancers world-wide, with some regional variations, e.g. HPV 16 and 18 account for 77% of cases in Oceania.³³

HPV can infect the entire genital tract, but there is a predilection for CIN and cancer to occur in the immature epithelium of the “transformation zones” in the cervix and anus.

While the traditional morphological spectrum CIN I to II to III is useful from a cyto/histopathology perspective, it is less useful in understanding the role of HPV in carcinogenesis since microscopic abnormalities are only seen in a minority of women with HPV DNA detected by DNA assay. From a practical perspective, e.g. natural history, CIN I and HPV should be viewed as similar lesions. HPV type, viral load and persistence are more important than the presence or absence of microscopic evidence of infection such as koilocytosis.^{34,35} Low viral load infections (e.g. detectable only by PCR) are less likely to be associated with microscopic changes and risk of subsequent precancer compared with high viral load infections.³⁶ The median time for clearance of prevalent infections varies from six months to one to two years, with 90% clearance of specific HPV types within two years.³⁴ Persistent infection is a marker for the development of CIN II and III. HPV 16 persists longer than other types, with an absolute risk of CIN III approaching 40% after five years’ persistence.³⁷ The previous view that the “high risk” woman (for developing CIN II or III and cancer) was the woman with a history of an early coitarche, multiple sexual partners etc, must now be replaced by the concept that persistent HR HPV infection is the most important risk factor.

CIN III must be regarded as the surrogate endpoint for cancer. However, CIN II lesions may represent severe cytological changes associated with HPV infection that are destined to regress while others are destined to persist with risk of progression. The median age of women with CIN III is 27-30 years. However, intensive prospective follow-up of women in their early 20s has demonstrated the rapid development of CIN II and III, often within a few months of incident infection.³⁸ Women with cervical screen detected invasive cancer are 10 years or more older than the median age of women presenting with CIN III.³⁴

Investigation of the role of co-factors for persistence and progression is difficult because of the ubiquitous and transient nature of HPV infection. While cigarette smoking,^{39,40} oral contraception⁴¹ and high parity⁴² have been consistently demonstrated as co-factors, the roles of oral contraceptives, other sexually transmitted infections and condom use is more equivocal.⁴³

HPV VACCINES

KEY POINTS

- **Both vaccines are safe and highly effective in preventing the HPV types associated with cervical cancer and precursor lesions caused by HPV types 16 and 18.**
- **Warts caused by HPV types 6 and 11 can be prevented by the quadrivalent vaccine.**
- **Ideally females should be vaccinated prior to sexual exposure.**
- **There is established efficacy of the vaccines in women up to 26 years.**
- **Vaccination in males and women over 26 years requires further definition.**

The principal reason for the development of HPV vaccines is the prevention of HPV-related lower genital tract malignancy, particularly of the cervix. The prevention of genital condyloma is a secondary consideration.

Virus like particles (VLPs) made of HPV L1 major capsid proteins are used in HPV prophylactic vaccines. VLPs are neither infectious nor oncogenic since they lack viral DNA. Therapeutic vaccines are still in development.

What HPV vaccines are available?

Merck & Co (Gardasil – marketed by Commonwealth Serum Laboratories [CSL] in New Zealand) and Glaxo Smith Kline (GSK – Cervarix) have both developed candidate vaccines. Gardasil, which obtained licensure in New Zealand in July 2006, contains VLPs for HPV types 6, 11, 16 and 18 and Cervarix VLPs for HPV types 16 and 18. Gardasil is licensed for use in females aged 9-26 and males 9-15 years. It is anticipated that Cervarix will be licensed later in 2007.

How effective are the vaccines?

In 2002, Koutsky et al reported the first randomised double-blind placebo-controlled trial of a monovalent HPV 16 VLP vaccine in 2400 young women.⁴⁴ This vaccine was 100% effective in preventing both HPV 16 infection and HPV 16-associated CIN for at least 3.5 years after vaccination.^{45,99} 7% of vaccinated women seroconverted, i.e. became anti-HPV 16 antibody positive.

The Merck quadrivalent vaccine (Gardasil) provides a high level of protection against persistent infection and disease associated with HPV types 6, 11, 16 and 18 through 30 months follow-up.⁴⁶ Phase 3 data from the FUTURE 11 trial demonstrated that Gardasil gave 96% protection against HPV 6, 11, 16 and 18 related persistent infection through five years follow-up.⁴⁷ In addition, none of the vaccine recipients developed type 6, 11, 16 or 18 related CIN II-III, cervical adeno carcinoma in-situ, vulval intra-epithelial neoplasia (VIN) II-III, vaginal intraepithelial neoplasia (VAIN) II-III or genital warts. Among women who are positive to one or more vaccine types 6, 11, 16 or 18, quadrivalent HPV VLP vaccine provides high level protection against disease related to the remaining HPV types.⁴⁷

Phase III data from the GSK vaccine (Cervarix) have demonstrated 100% efficacy against persistent infection and 93% against cytological abnormalities associated with HPV 16 and 18 with follow-up extending to 4.5 years.^{48,49} This study raised the possibility of protection against related HPV genotypes.

How safe are these vaccines?

Both vaccines are safe and well tolerated, the majority of adverse events (94%) were reported as mild or moderate, with injection site reactions the most common.⁵⁰ No serious adverse reactions have been reported.

Who should be vaccinated and when?

Both HPV vaccines, Gardasil and Cervarix, are recommended for females between 9 and 26 years, ideally prior to starting sexual activity and exposure to the virus. As noted above, only Gardasil is licensed at this time but Cervarix is likely to be licensed later in 2007. Since there is a scheduled vaccination at 11 years, this may be an optimum time to administer the vaccine. The vaccines are generally administered on day one, month one to two, and month six.

Even if a woman has been exposed to one or more HPV types, the vaccine will protect against other types covered by that vaccine.

These vaccines have no therapeutic effect, i.e. patients with established genital warts or CIN caused by the relevant HPV vaccine type will not benefit from the vaccine.

Although Gardasil is licensed for males 9 to 15 years, the role of vaccination in this group is unclear and current research is underway to determine this.

Gardasil is not licensed for women over 26 years, but research is also underway to determine the role of HPV vaccination in this group.

How long will they last?

The vaccines are highly immunogenic, and although the duration of immunity is unknown, stable protection has so far been observed for five years.⁵⁰ Even when there are no detectable antibody levels, the immune memory mechanism may provide long term protection.

Will cervical screening still be needed?

Yes. Irrespective of whether a woman has been vaccinated, routine cervical screening will need to continue for the foreseeable future. This is because of possible prior infection with HPV types causing CIN, or new infection with other HPV types not covered by vaccination.

The vaccine and pregnancy

These vaccines are not recommended for use in pregnancy. Completion of the vaccine course should be deferred if a woman is found to be pregnant. There is no evidence from the clinical trial that administration of the Gardasil vaccine adversely affects fertility, pregnancy, or infant outcome.

Will less common genotypes replace types 16 and 18?

In theory, widespread vaccination may allow less common genotypes to replace the vaccine types but expert opinion believes this to be unlikely.⁵¹

CLINICAL PRESENTATION AND DIAGNOSIS

(See page 30 for clinical photographs)

Subclinical HPV infection is asymptomatic and usually diagnosed by finding cytological abnormalities consistent with HPV infection on a cervical smear or by HPV viral detection methods.⁵²

Genital warts are visible lesions that occur in the anogenital area and there is good correlation between physical findings and histological studies. They appear as discrete lesions or may coalesce into confluent plaques. They may be skin coloured, red, white or brown. Smooth papular warts tend to occur on fully keratinised skin (labia and shaft of penis), condylomata acuminata occur most commonly on moist mucosal surfaces, and flat-topped papular external genital warts can occur on either surface. Genital warts are frequently multifocal (one or more lesions at one anatomic site, e.g. vulva), or multicentric (lesions on disparate anatomic sites, e.g. perineum and cervix).⁵³⁻⁵⁵ It is important to examine the entire lower genital tract for the presence of multicentric visible warts before treatment.

Evaluation for intra-anal warts by anoscopy is recommended for men and women with recurrent perianal warts and/or a history of receptive anal intercourse. Urethromeatoscopy using an auroscope may help assess meatal warts in males.

Differential diagnosis

The differential diagnosis of genital warts in women includes lesions which cause papules, plaques and flat erythematous lesions. Genital papules include normal anatomic structures such as vestibular papillae and sebaceous glands (Fordyce spots). Acquired papules and plaques include seborrhoeic keratoses, molluscum contagiosum, psoriasis, lichen nitidus, lichen planus, skin tags, melanocytic nevi, angiomas and condylomata lata.

Vulvar intraepithelial neoplasia (VIN) usually presents as white, red or pigmented papules or plaques which may be pruritic, but can be asymptomatic. The lesions may have a warty surface and can be unifocal or multifocal. A lesion may be small and discrete or may be an extensive plaque covering most of the vulva or perianal skin. It may be clinically indistinguishable from the papular form of external genital warts, but appears more disorganised.^{56,57} Histological examination of these lesions shows high-grade intraepithelial neoplasia: VIN is usually associated with HPV type 16 infection.^{20,21}

In men, papular lesions other than warts include sebaceous glands (Tyson's glands), pearly penile papules (angiofibroma), and Bowenoid papulosis (a type of in situ neoplasia which usually resolves spontaneously). Flat erythematous lesions include psoriasis, seborrhoeic dermatitis, lichen planus, Zoon's plasma cell balanitis, balanitis circinata associated with Reiter's syndrome, and in situ neoplasia of penile intraepithelial neoplasia (PIN) skin.

Three clinical variants of PIN are recognised: Erythroplasia of Queyrat, (red patches of the glans penis and foreskin), Bowen's disease, (scaly patches and plaques) and Bowenoid papulosis. Many are associated with HPV type 16.⁵⁸

MOLECULAR (DNA) DIAGNOSIS OF GENITAL HPV INFECTION

Virological diagnosis of HPV relies on detection of viral DNA. A variety of DNA detection methods are available. Polymerase chain amplification (PCR) of a short region of specific viral DNA is probably the most sensitive method but may not be the most appropriate method for cervical screening purposes.⁵⁹ Other commercial detection methods are available, the most widely used being Digene Hybrid Capture System which detects the 13 most common oncogenic types.

Infection with HPV is a necessary but not sufficient pre-requisite for the development of cervical carcinoma. It follows therefore that sensitive DNA detection methods which can detect HPV infection with a high degree of reliability are very valuable for assessing the risk of progression to carcinoma. In studies of women with indeterminate cervical smears (category Abnormal Squamous Cells of Uncertain Significance (ASC-US)), a NEGATIVE result for HPV DNA clearly identifies a very LOW risk of progression. At present, these women are recalled at six month intervals or sooner for repeat cervical cytology.

Routine screening for HPV DNA should NOT be offered to women under 30 years of age. These younger women may have multiple repeat episodes of HPV infection, usually associated with minor cytological changes. The natural history of the disease in this age group is usually clearance of viral infection and resolution of the cytological changes. Detection of what is likely to be transient HPV infection is not helpful and may generate considerable anxiety.

Conversely, in older women, detection of high-risk oncogenic papillomavirus signals the potential for significant underlying pathology and such women should be referred for colposcopy.

Commercially available HPV testing

At the time of writing these guidelines, HPV testing and typing has not formally been incorporated into the New Zealand cervical screening programme. In other countries, such tests are being increasingly recognised as contributing to improving the diagnosis of cervical pathology. The most common methods of HPV testing are Digene's Hybrid Capture® technology and polymerase chain reaction (PCR) techniques. Digene's test for high-risk types of HPV was approved by the FDA in the United States in March 2003 and is also widely used in Australia as an adjunct to cervical screening. Version hc2 detects the 13 most prevalent oncogenic HPV types.

In New Zealand, the cost/benefit of including HPV DNA testing in the cervical screening programme screening is currently being evaluated. For ongoing information about this we recommend the National Cervical Screening Programme (NCSP) "Guidelines for the Management of Women with Abnormal Smears", currently being revised and due out later in 2007.

Summary – DNA testing for high-risk oncogenic HPV

1. Helpful in the assessment and accurate triaging of women over 30 years of age with ASC-US.
2. Should not be offered to women under 30 years of age unless unusual circumstances prevail.
3. Currently is not recommended as a routine accompaniment to all cervical screening in New Zealand. In Australia, HPV DNA testing is used post-treatment as “test of cure” as per the National Health & Medical Research Council (NHMRC) guidelines, “Screening to Prevent Cervical Cancer: Guidelines for the Management of Asymptomatic Women with Screen Detected Abnormalities”.

Samples required for HPV DNA detection and typing

1. Digene HPV test. Specimens are collected using a broom-type collection device and rinsed into the supplied transport medium.
2. Endocervical swab or cytobrush sample. Send to laboratory in swab “sleeve”. Alternatively, the swab or cytobrush may be suspended in a small vial with approximately 1ml of sterile normal saline. The shaft of the swab or cytobrush should be cut with a sterile disposable scalpel blade.
3. Liquid-based cytology sample (Thin Prep or Cytospin). An aliquot of this sample should be stored at 4°C. It is essential that adequate cells be present in this aliquot, i.e. centrifuged supernatant is totally unsuitable.

TREATMENT OF GENITAL HPV INFECTION AND GENITAL WARTS

KEY POINTS

- The primary goal of treatment is to eliminate warts that cause physical or psychological symptoms. No treatment is an option for asymptomatic warts and the cure should not be worse than the disease.
- There is no definitive evidence that any one treatment is superior than the others and no single treatment is suitable for all patients or all warts.⁶⁰
- The method of treatment should be determined by patient preference, available resources and the experience of the practitioner. Other factors include the size, number and site of the warts, the age of the patient and whether the patient is pregnant.
- Commonly used treatments in primary care are self-administered podophyllotoxin or imiquimod and practitioner administered cryotherapy.
- If there is no significant response within four to six weeks, an alternative diagnosis, change of treatment modality or onward referral should be considered.
- Patients should be given information about all the treatment options in order for them to make an informed decision about their preferred choice.

Subclinical infection

There is no specific treatment for subclinical HPV infection, which is usually temporary and resolves spontaneously.⁶¹ Women who have cervical HPV infection should have follow-up cervical smears as advised by their health care providers in accordance with the National Cervical Screening Guidelines.

Genital warts

There is a wide overlapping range of reported response rates and recurrence rates for individual treatments, and few comparative trials making evidence-based choices of treatment difficult.⁶² At present there is no ideal treatment for all patients or all warts and spontaneous resolution may occur. 20% may resolve spontaneously in six months.⁶³ A cohort study in men demonstrated that although there was no significant difference in the time to cure between those who received treatment compared to those who were not treated, there was a significant decrease in the number of warts and fewer new lesions appeared.⁶²

The primary goal of treatment is to eliminate warts that cause physical or psychological symptoms. Physically, warts are often asymptomatic but can be painful, friable or pruritic. Emotionally, warts may be socially stigmatising or aesthetically upsetting.

Although treatment can result in a clinically free state, the underlying viral infection may or may not persist. The elimination of external visible warts may not decrease infectivity since the warts may not represent the entire viral burden as internal sites and clinically normal skin may act as reservoirs for HPV infection. Warts rarely progress to cancer.

Treatment should be discussed with the patient and tailored to their infection and needs, as well as to available resources.

Patients should be given information about all treatment options (including no treatment) in order for them to make an informed decision about their preferred choice.

Not all treatments are funded and the availability of some options may be restricted.

Presentation may also influence treatment choice, with warts on moist, partially keratinized surfaces and intertriginous areas responding better to topical treatments than do warts on dry, fully keratinized surfaces and open areas. Aggressive ablative therapy should be avoided over the clitoris, glans penis, urinary meatus, prepuce and prepuccial cavity in uncircumcised men. Perianal warts, and often genital warts in women, as they cannot be adequately visualised, are not suitable for application of podophyllotoxin.

For a summary of treatment by anatomic site and treatment options, see tables 1 and 2, page 18-19.

Self-applied treatments (home therapy)

Self-applied treatments include the immune enhancer imiquimod (Aldara™) cream and the chemical ablative podophyllotoxin (Condylina™ solution and Warticon™ cream). These are first line treatments in the United States.¹ Patients must be able to follow application instructions, to successfully use these therapies and careful explanation of their use is important. **Higher than recommended doses of both of these applications may lead to an increase in adverse skin reactions.**⁶⁰

Imiquimod

Mechanism of action: An immune enhancer that stimulates production of interferon and other cytokines. It appears to have an advantage of reduced recurrence rate.

Suitable for: Women, and some men with foreskin-associated warts. Particularly useful for 'carpet warts', e.g. female introitus and perianal area.

Contraindications: Not currently recommended in pregnancy. A register of imiquimod use in pregnancy has been established.*

Application: Careful application of imiquimod cream is important.

Applied onto fingertip and rubbed onto clean dry, wart area until cream vanishes once daily, three times per week, prior to normal sleeping hours and after sexual activity (imiquimod weakens condoms and vaginal diaphragms). Wash off next morning or after 6-10 hours.

The manufacturer recommends that a sachet be used for single use to cover an area of up to 20cm². However, it has been demonstrated that one sachet will cover up to 386cm² and although, not recommended by the manufacturer, one sachet is commonly used for multiple applications.⁶⁴ It is recommended that treatment should be continued until the warts have resolved, or up to a maximum of 16 weeks per course.

A preliminary study involving a small number of largely pre-treated women showed that a four week course of imiquimod was as effective as longer courses of 8, 12 and 16 weeks with fewer adverse reactions and reduced cost.⁶⁵ The majority of women who cleared their warts did so by eight weeks regardless of the duration of treatment, suggesting that imiquimod prompts a cell-mediated response with specific T-cell immune memory within the first four weeks.

Side effects: Localised erythema, swelling and/or rarely superficial ulceration of the treated area can be expected from two to six weeks as part of the immune response and will probably be related to the direct therapeutic action of the agent, i.e. switching on the immune response rather than to hypersensitivity. If indicated, the clinician may advise the patient to miss the next two applications, use salt water baths as well as drying with a hairdryer before recommencing treatment. These local skin reactions cause discontinuation of the treatment in less than 2% of patients.

* 3M Monitoring System in Pregnancy:
Pharmacovigilance Unit, 3M Health Care Ltd, Morley Street, Loughborough, Leicestershire, LE11 1EP, UK.

Podophyllotoxin

Podophyllotoxin is dispensed in two forms, as a 0.5% solution (Condyline™) and as a 0.15% cream, (Warticon™). These contain purified podophyllin in a more standardised form. Podophyllotoxin has been extensively studied in randomised and placebo-controlled trials.

Mechanism of action: The active moiety is an antimitotic and causes localised tissue necrosis. Localised epidermal pallor, caused by intracellular oedema, can usually be seen within 48 hours of application.

Suitable for: Small external warts which can be visualised. May be less effective for keratinised warts.⁶⁰

Contraindications: A history of hypersensitivity (incidence approximately 1%). They are not used in pregnancy or lactation, or in children. Should not be used on warts which cannot be visualised, on internal warts and they are not recommended for extensive wart areas (>10cm²).

Application: Patients must be able to visualise, identify and reach their warts, and if necessary should be shown what is wart and what is normal skin, using a mirror. Podophyllotoxin solution should be applied carefully to the warts using one of the applicators enclosed with the product, taking care that the solution does not come into contact with healthy skin and allowing drying after application to avoid inadvertent spreading of the solution. Applying Vaseline or zinc ointment on healthy skin around the wart(s) can be protective. The cream Warticon™ is applied directly by finger and may be more easily applied by women and in the treatment of perianal warts. The solution or cream should be applied twice daily for two to three consecutive days each week until the warts have resolved, or for a maximum of five consecutive weeks.

Side effects: Mild erythema with slight pain and/or superficial ulceration of the treated area can be expected. More severe skin ulceration, erosions, erythema, irritation, scarring; phimosis, pain, burning and soreness can occur. These effects are usually only mild to moderate in severity and resolve when the warts necrose.⁶⁰

Physician-applied treatments

Cryotherapy

Mechanism of action: Destroys the wart tissue by freeze/thawing resulting in sloughing and wart destruction.

Suitable for: External and internal warts. Dry and moist warts. Can be used in pregnancy.

Contraindications: Cryoglobulinaemia.

Application: Adequate training and expertise in this technique is required. Effective cryotherapy may be achieved by a cryoprobe or application of liquid nitrogen by spray or by loosely wound cotton on a wooden applicator (not with tightly wound, typical cotton swabs). The full thickness of the wart should be frozen until there is whitening of the surrounding skin area for 2mm. Treatment is repeated weekly until the warts have resolved. Most sexual health clinics have facilities for more focused freezing using fine probes with nitrous oxide or carbon dioxide cryoguns. Patients can be referred for treatment.

Side effects: Pain and necrosis following application of cryotherapy are fairly universal, and blistering may occur. The treatment of large warts or areas at one time can create wound care problems. Adverse effects include balanoposthitis, irritation, local oedema, necrosis, ulceration and pain, especially when the treated area thaws. Both hypo- and hyperpigmentation can occur but this is usually temporary. Although the use of injected local or topical anaesthesia (e.g. Emla cream) is rarely necessary, it may facilitate cryotherapy by reducing pain when a large number or area of warts are present.

Curettage and scissor or scalpel excision

Mechanism of action: Directly remove genital warts

Suitable for: Exophytic warts

Contraindications: Known bleeding abnormality. Can be used in pregnancy.

Technique: Direct removal with extension of the wound only into the upper dermis. Haemostasis can be secured with an electrosurgical unit or a chemical styptic (e.g. silver nitrate sticks); suturing is rarely required or indicated when removal is done properly.

Side effects: Localised pain, for which mild analgesics may be required, and bleeding. If operating-room surgery is required there are the additional hazards of a general anaesthetic.

Electrocautery or diathermy (Hyfrecation)

Mechanism of action: Coagulates proteins of treated tissues.

Suitable for: Anogenital and oral warts.

Contraindications: None. Can be used in pregnancy.

Technique: Requires advance training and expertise to minimise scarring. Once anaesthesia is attained, physical destruction of warts. Usually, no additional haemostasis is required.

Side effects: Local pain and possible infection. Scarring is more common than after cryotherapy.

Laser therapy

Mechanism of action: Vaporisation of warts.

Suitable for: Vulval, vaginal, cervical and perianal warts. Not considered first line because of expense. Can be considered if there are obstructive lesions.²⁸ For large lesions, can be combined with electrocautery.

Contraindications: None. Can be used in pregnancy.

Technique: Adequate training required. Dermal tissue destruction should be limited to 1mm.²⁸

Side effects: Local pain. Scarring and hypo- or hyperpigmentation can be minimised by controlling depth and avoiding treatment beyond the dermal papillae.

Podophyllin resin

Podophyllin is no longer recommended as a treatment for genital warts. It has a higher incidence of adverse reactions and reduced efficacy when compared to podophyllotoxin.

Trichloroacetic acid (TCA)

Mode of action: TCA is a caustic agent that destroys warts by chemical coagulation of proteins. Treatment solution concentrations have not been standardised and saturated concentrations of 85-95% have been used.

Suitable for: Small warts on moist surfaces.

Application: Training is necessary before applying this treatment. TCA solutions should be applied sparingly and allowed to dry before the patient sits or stands. If there is intense pain, the acid can be neutralised with soap and sodium bicarbonate. TCA solution has a low viscosity (comparable to that of water) and, if overapplied, can spread rapidly and "run", damaging a significant area of normal tissue.

Contraindications: Nil but most suitable for small moist warts. Can be used in pregnancy.

5% flurouracil cream

Not recommended for routine warts because of unproven efficacy, significant toxicity, and teratogenicity. Currently a specialist-only medication. Adverse effects of dysuria, epithelial and urinary meatal erosion, erythema, eschar, hyperpigmentation, local irritation, burning, and itching have been reported.

Systemic interferon

Not recommended because of expense and side effects and poor efficacy. However, the efficacy of pegylated interferon was demonstrated in one small controlled study in HIV positive patients.⁶⁶

Future treatment modalities

Cidofovir

Mechanism of action: Inhibition of cellular proliferation.

Suitable for: Warts resistant to treatment. Results of a Phase 2 double blind trial have been reported,⁶⁷ confirming efficacy and safety.

Application: Extemporaneously prepared gel as 1% formulation.

Contraindications: Not advised in pregnancy as no data.

Other innovative approaches

Small trials and case series have been reported using the following:

- Photodynamic therapy with 5 aminolaevulinic acid.⁶⁸⁻⁷⁰
- The application of bacillus Calmette Guerin polysaccharide nuclear acid following CO₂ laser resection.⁷¹
- Application of viable bacille Calmette Guerin topically as a potential therapeutic modality in condyloma acuminata: a placebo controlled study.⁷²
- Oral isotretinoin.⁷³

Therapeutic vaccines for HPV infection: Early phase studies of vaccines to treat existing HPV infection are being conducted in many centres. Results to date have shown vaccine safety but in most studies there has been limited evidence of efficacy, and there is no consensus product. Thus, there can be no certainty that therapeutic vaccines will be developed in the foreseeable future.

Selecting treatment(s) for individual patients (see table 3, page 20).

Many patients require a course of therapy rather than a single treatment. Studies have not systematically evaluated the factors that influence the selection of therapy although a survey found that patients expressed a desire for topically applied therapies that can be used at home. **As no one treatment is ideal for all patients or all warts, consideration should be given to a change of treatment modality or onward referral if there is no significant response within four to six weeks. Usually patients require a course of therapy, rather than a single treatment.**

Most treatment modalities are eventually effective in eliminating small numbers of warts. Patients with limited disease (i.e. one to five warts) may benefit most from cryotherapy or simple office surgery. Ablative therapy should be considered in those with large or extensive areas of warts to at least debulk their warts.

For self-applied therapeutic modalities, treatment beyond the manufacturer's recommendations is not advisable and concurrent use of multiple therapeutic modalities on a single wart is not recommended as routine treatment. **It should be borne in mind that a continuing lack of response to therapy might indicate other pathology and referral for assessment should be considered in such cases.**

Continually evaluate the response to treatment to avoid over-treatment and a therapeutic course worse than the disease itself. Persistent hypo- and hyperpigmentation is a possible complication of ablative therapeutic modalities. Depressed or hypertrophic scars rarely occur. Ablative treatment, especially to the introitus, can result in disabling chronic pain syndrome (e.g. vulvodinia/vestibulitis) or hyperaesthesia at the treatment site.

Surgical removal of warts, by diathermy, laser ablation or excision under local or general anaesthesia, may render the patient wart-free, usually in a single visit. However, the disadvantages are that significant training, a moderate amount of equipment, and a longer patient visit are required. Although surgery is obviously of most benefit when warts are present in large numbers or over large surface areas, it can be used for average cases. While the cost of a single surgical visit may be greater, surgery can be accomplished in one visit what other ablative modalities often require multiple visits to accomplish which may result in greater cost-effectiveness for some patients. However, recurrence rates may be the same as other therapeutic modalities and the morbidity of treatment may be greater with increased risk of pain, infection and scarring.

Combination treatment

Although treatments are commonly combined, few studies have been published which support this practice. It has been shown that TCA and podophyllin in combination reduce the number of treatments to achieve clearance compared to TCA alone.⁶² A combination of laser and imiquimod has been shown to be safe and well tolerated.⁷⁴

Symptomatic therapy

- For ongoing management by the GP or health professional, the patient should be advised to return weekly for treatment until all the warts have gone. Patients may be referred to a specialist or sexual health clinic when there is a poor response to treatment or warts continue to recur after three months.
- Saltwater baths are the single most useful thing the patient can do to help soothe and heal the genital area during treatment. Two handfuls of plain salt per bath or two tablespoons in a large bowl, preferably twice daily, and dry with hairdryer.
- Lignocaine gel 2% (Xylocaine™) is a useful local anaesthetic to put on raw areas two minutes prior to micturition and defaecation.
- A concomitant thrush infection is common. Local imidazole preparations often help.
- For large areas made raw by wart ablations, 1% silver sulphadiazine cream is useful.

Post-treatment follow-up

The benefit, frequency, interval and type of follow-up care necessary after the treatment of warts has not been studied. Follow-up evaluation can provide the opportunity for education and counselling of patients. The need to monitor for complications of therapy will vary greatly on the basis of the patient's experience and cognitive ability, the number and location of warts, and the treatment modality used. Patients concerned about recurrences could be offered an evaluation three months after successful treatment, since most recurrences occur during this period. In immunosuppressed patients, recurrences of warts are much more common and periodic follow-up evaluation may be necessary.

Patients with genital warts are at risk of other sexually transmitted infections (STIs). Management of genital warts must include careful assessment and testing for other STIs as appropriate, depending on the patient's sexual history.

Treatment recommendations

- The goal of treatment for genital warts is the removal of visible warts. **GRADE C**
- Standard therapies for genital warts can eventually remove most warts, although no one treatment is ideal for all warts or all patients. **GRADE A & C**
- Clinicians should be knowledgeable about, and have available to them, at least one patient applied treatment and one health care provider administered therapy. **GRADE C**

Assessment of sex partners

Sex partners of patients who have genital warts may benefit from examination to assess the presence of genital warts and other sexually transmissible infections, although a specific test for subclinical HPV is not currently available in New Zealand. Sex partners may benefit from counselling about the implications of having a partner who has genital warts. The use of condoms may reduce, but does not eliminate, the risk of transmission to uninfected partners. Female partners of patients who have genital warts should be reminded that cytological screening for cervical cancer is recommended for all sexually active women who have ever had sexual intercourse.

Similarly, the specific benefit of evaluating sex partners of women with HPV-related cervical squamous intra-epithelial lesions (SILs) for external genital warts is not known. Although as many as one-half of male sex partners of women with cervical SILs may have evidence of genital HPV infection, relatively few have external genital warts. It is unclear whether treatment of men with evidence of genital HPV infection influences the natural history of their female sex partner's cervical disease.^{75,76} There is little information available currently about the health effects of HPV-related cervical disease on female sex partners of women with HPV infection.⁷⁷ Women who are sex partners of patients with external genital warts should undergo cytological screening for cervical cancer at intervals recommended by national cervical screening guidelines. The benefit of evaluating male sex partners of men with external genital warts is not known.

Table 1 Treatment by site

(For details of individual therapies, see Table 2)

Site	Treatment	Use in Pregnancy
External genital warts	Patient applied Podophyllotoxin solution or cream OR Imiquimod 5% cream.	No
	Provider administered Cryotherapy OR Trichloroacetic acid OR Surgical removal OR Laser OR Diathermy.	Yes
Cervical warts (high grade CIN excluded) Vaginal warts	Cryotherapy with liquid nitrogen. Cryoprobe not recommended in vagina because of risk of vaginal perforation/fistula formation. However, the experienced operator can use a bent Cryoprobe with protective sleeve (to stop sticking to the vaginal wall) OR Trichloroacetic acid.	Yes
Urethral meatal warts	Cryotherapy with Cryoprobe (technically difficult with liquid nitrogen). N.B. risk of stenosis if over zealous treatment. Note: Podophyllotoxin and imiquimod have been used but limited data.	Yes
		No
Anal warts	Cryotherapy. Special open sided anosopes and bent probes are available to permit treatment laterally OR Surgical removal.	Yes
Oral	Cryotherapy OR Surgical removal.	Yes

Table 2 Summary of treatment options

Note: All treatments have wide response and recurrence rates. Not all treatments are funded in New Zealand.

Forms of Treatment	Usage	Application Frequency/Duration	Advantages and Disadvantages	Use in Pregnancy
Patient applied				
Imiquimod 5% cream Aldara	External genital warts	Patient should apply once daily at bedtime, three times a week for up to 16 weeks. The treatment area should be washed with soap and water 6 to 10 hours post application.	Immune enhancer. May be more effective on moist warts e.g. introitus and perianal areas. Relatively low recurrence rate.	Not recommended. If used, should be registered with 3M monitoring system.*
Podophyllotoxin. Condyline (solution) or Wartec (cream).	External genital warts	Patient should apply podophyllotoxin solution with the supplied applicators, protecting surrounding skin with Vaseline. The cream is applied with a finger, to visible external warts, twice a day for 3 days, followed by 4 days of no therapy. This cycle may be repeated, as necessary, up to 4 cycles. The total wart area should not exceed 10cm ² , and the total volume of podophyllotoxin solution should not exceed 0.5 ml/day. If possible, the initial treatment should be demonstrated by the health care provider.	Results are dependent on patient compliance and correct application of treatment. Not for large (>10 sq cm) wart areas and may be less effective on dry warts. Over zealous use can cause painful ulceration. The solution should be used on readily visible warts, particularly in men. The cream preparation may be preferable in women in hard to reach areas.	No

* 3M Monitoring system in Pregnancy:
Pharmacovigilance Unit, 3M Health Care Ltd, Morley Street, Loughborough, Leicestershire, LE11 1EP, UK.

Table 2 Summary of treatment options

Continued

Forms of Treatment	Usage	Application Frequency/Duration	Advantages and Disadvantages	Use in Pregnancy
Provider-administered				
Cryotherapy (Cryoprobe or liquid nitrogen on prepared swabs)	External anogenital, cervical, urethral, anal or oral warts	Weekly. Freeze full thickness of wart, whitening the surrounding skin area up to 2mm. The size of the swab should be tailored to the size of the lesions e.g. use of orange stick and wrap around cotton wool to obtain correct size.	Effective for moist and dry warts, pain can be reduced by use of local anaesthetic, gel/cream. Safety and efficacy highly dependent on skill level, equipment and experience. Risk of over or under application with liquid nitrogen.	Yes
Electrocautery or diathermy (Hyfrecation)	External anogenital or oral warts	Single treatment.	Prompt wart free state, results depend on skill level and training, requires equipment, longer clinic visit, local anaesthesia is mandatory. Skin bridges should be left in between sites to aid healing and minimise scarring.	Yes
Laser therapy	Extensive anogenital warts	Single treatment.	Prompt wart-free state, may require general anaesthetic. Expensive and only available in a few major centres.	Yes
Surgery	Extensive anogenital, oral or anal warts	Removal by tangential scissor excision, tangential shave excision, curettage or electrosurgery. Treatment can be repeated as required.	Prompt wart free state, results depend on skill level and training, requires equipment, longer clinic visit. Anaesthesia mandatory. Particularly useful for pedunculated warts, and small numbers of anatomically accessible warts.	Yes
Trichloroacetic acid (TCA)	External anogenital, vaginal or anal warts	A small amount should be applied only to warts and allowed to dry, at which time a white "frosting" develops. If an extra amount of acid is applied, the treated area should be powdered with sodium bicarbonate, or liquid soap preparations to remove unreacted acid. Surrounding skin can be protected with petroleum jelly. Can be repeated weekly as required.	Inexpensive, effective for moist and dry warts. Needs careful application by a trained health professional. Not for large areas of friable warts. Low viscosity may result in spreading if over applied, which can cause painful iatrogenic ulceration.	Yes

Note: 5-fluorouracil and interferon have been used for treatment of genital warts. However, the use of the former is limited by severe local side effects and of the latter by side effects and expense and are therefore seldom used.

Table 3 **Factors that may influence the selection of treatment for warts**

Patient preferences and characteristics
Preference for self-applied or administered treatments.
Ability to identify accurately and physically reach warts.
Cognitive ability.
Cost of treatment.
Duration of treatment and/or number of visits, distance and work.
Tolerance of pain.
Age
Safety and efficacy of treatments for warts have not been studied in paediatric populations.
When treating, attention should be paid to avoiding and controlling pain associated with treatment. Requiring a parent or guardian to apply a treatment that may be painful is questionable.
Variations in the rate of psychosocial development in adolescence should be taken into account (i.e. cognitive ability to understand and carry out any treatment program, particularly patient-applied therapy).
Pregnancy
Podophyllotoxin is not recommended and the safety of imiquimod in pregnancy is not known. 5-fluorouracil is a teratogen.
Disease presentation
Wart size and count: in general, provider administered topical treatments are not ideal for large areas of warts, although they may have a debulking effect.
Anatomic location and circumcision status (men): Warts on moist (partially keratinised) surfaces and intertriginous areas appear to respond better to topical treatments than do warts on dry (fully keratinised) surfaces and open areas. Aggressive ablative or surgical therapy should be avoided over the clitoris, glans penis, urinary meatus, prepuce, and prepuccial cavity in uncircumcised men.
Health care provider preferences and characteristics
Clinical training and experience.
Financial and physical resources.
Scheduling limitations.
Immunologic status
Immunocompromised patients may have lower response and higher recurrence rates.

SPECIAL SITUATIONS

Pregnancy

KEY POINTS

- **Although genital warts are common in pregnant women, it is rare for babies to develop clinical HPV.**
- **Transient HPV colonisation in the neonate is common, but persistent infection is unusual.**
- **Recurrent respiratory papillomatosis is a rare but serious complication of HPV infection in the neonate.**
- **Ablative methods e.g. cryotherapy or diathermy, should be used for treatment of genital warts in pregnancy.**
- **Caesarean section has not been shown to significantly reduce maternal fetal transmission and should be reserved only for outlet obstruction.**

Genital warts can proliferate and become friable during pregnancy, due to the altered immunity as well as increased blood supply. Their removal during pregnancy is often requested by the patient and can be attempted with cryotherapy up to delivery.⁷⁸ It is not unusual if left untreated for the warts to clear spontaneously post-delivery. HPV types 6 and 11 can, rarely, cause laryngeal papillomatosis in infants and children. A Danish study reported an incidence of 7 per 1000 where there was a documented history of external genital warts, a rate which was 135.3 times higher than where there was no history of external genital warts.⁷⁹ A review article states that the overall incidence is 3.5 per million person-years and the prevalence is four cases per 100,000 children.⁸⁰ In babies born to mothers with genital warts, HPV DNA will be isolated from aerodigestive swabs in a third to a half but the risk of development of RRP is roughly 1 in 400. Presentation can be at any age, but typically it is at three to four years with progressive hoarseness. An earlier presentation is often associated with a poorer prognosis, because of multi-centric disease.

Although there appears to be an association between maternal genital warts during vaginal delivery and laryngeal papillomatosis, the route of transmission (transplacental, perinatal, or postnatal) is not completely understood. HPV DNA has been detected in amniotic fluid, raising the possibility of ascending infection, and HPV DNA has been detected in the peripheral blood mononuclear cells of mothers and in cord blood samples,⁸¹ Although this may suggest transmission via a haematogenous route, transmission via microscopic tears in the placental membranes, as occurs with other organisms, is a more likely explanation.⁸² There has been a wide variation in reported neonatal transmission rates for HPV, although larger studies using more recent HPV DNA technology indicate that transmission rates are low.^{36,37} In a study of 574 women, 47.1% were identified as being HPV DNA positive (mainly in the third trimester) at age ≤ 24 and 24.4% at age >24 . However, 1.6% of newborns were HPV DNA positive at a mean of 65 hours after birth.⁸³ Non-concordance between parental and neonatal HPV types suggests the possibility of maternal infection acquired antenatally at untested intervals during pregnancy, or in the case of oral infection from other contacts after birth.⁸³ Follow-up studies of infants from whom HPV DNA was isolated at birth indicate that the virus becomes undetectable in many infants, indicating that contamination rather than true infection has occurred.⁸⁴ It has also been demonstrated that HPV 16 antibodies detected at birth will clear from the infant within 10 months, but not from the mother.⁸⁴

In summary, although HPV infection is frequently detected in pregnant women, detection of HPV in newborns is uncommon and is likely to be due to contamination rather than to persistent infection.

Although caesarean section reduces the risk of HPV isolation from the neonate, it has not been shown to significantly reduce neonatal transmission of HPV, nor of laryngeal papillomatosis.⁷⁹ Many studies have been limited by lack of long term follow-up and assessment of only HPV positivity rates after birth.⁸⁵ Caesarean delivery should not be performed solely to prevent transmission of HPV infection to the newborn. In rare instances caesarean section delivery may be indicated for women with genital warts if the pelvic outlet is obstructed or if vaginal delivery would result in excessive bleeding.

Treatment during pregnancy requires some special considerations. Podophyllin and podophyllotoxin should not be used in pregnancy. Maternal and fetal deaths have been reported following the use of podophyllin for large vascular warts. Imiquimod is not recommended as there is insufficient data to recommend its use in pregnant women. Individual case reports and a small case series have been published but usage of imiquimod should be reported to the register of imiquimod use in pregnancy which has been established.^{86*} Appropriate treatments of external genital warts during pregnancy include cryotherapy, TCA, or surgical removal and laser ablation.

HPV in pregnancy has no link with miscarriage, premature labour or other types of pregnancy complications.

Treatment recommendations

- Podophyllin and podophyllotoxin should not be used in pregnancy. **GRADE C**
- Caesarean section does not significantly reduce vertical transmission and is only indicated when genital warts are likely to cause obstruction of the pelvic outlet or excessive bleeding. **GRADE B**

Breastfeeding

The use of podophyllin and podophyllotoxin are not recommended in women who are breastfeeding because of systemic absorption. The use of imiquimod is not recommended because of insufficient data. Trichloroacetic acid, cryotherapy, electrocautery and laser can be used during lactation.

Immunosuppressed patients

Persons who are immunosuppressed because of HIV or other reasons may not respond as well as immunocompetent persons to therapy for genital warts, and they may have more frequent recurrences after treatment. Immunosuppressed women should have cervical smears annually, with early referral for colposcopy if abnormalities are detected. Squamous cell carcinomas arising in SILs resembling genital warts occur more frequently among immunosuppressed persons.

Adolescents

Variations in the rate of psychosocial development of adolescents should be taken into account (i.e. cognitive ability to understand and carry out any treatment programme, particularly patient-applied therapy).

* 3M Monitoring System in Pregnancy:
Pharmacovigilance Unit, 3M Health Care Ltd, Morley Street, Loughborough, Leicestershire, LE11 1EP, UK.

KEY ISSUES IN COUNSELLING

Genital HPV infections are common in people who are sexually active. However, conditioning and social values contribute to individuals having a wide range of emotional responses when given a diagnosis of genital HPV.

Emotional feelings related to the diagnosis of genital HPV

- Guilt
- Embarrassment
- Sense of isolation
- Loss of assertiveness
- Unworthiness
- Sense of injustice
- Surprise
- Shock
- Dirtiness
- Anger
- Confusion
- Fear
- Denial
- Grief
- Loss of sex life

Good therapeutic management acknowledges these emotional responses and addresses the person's feelings and concerns. Counselling plays an important role and can significantly assist patients with the adjustment of being diagnosed with viral sexually transmitted infection.^{87,88} These issues should be addressed at the first presentation. Not all patients will want to take up the offer of counselling and support. Nevertheless, it is important to offer it to all patients so that they can make this decision.

The patient who presents with genital HPV for the first time may feel very vulnerable. It should be acknowledged how difficult it must have been for the person to present for treatment.⁸⁹⁻⁹¹ Sometimes the diagnosis is unexpected. The health professional/counsellor should never be dismissive of the patient's disease; for some patients, a diagnosis of genital HPV may be the most challenging health disruption they have experienced, given the stigma associated with sexually transmitted infections. It is important to show empathy and allow time to talk. Counselling and education about genital HPV should take place in an appropriate setting. The following points should be considered:

- Comfortable setting
- Patient dressed
- Minimal interruptions
- Confidentiality assured
- Adequate time
- Attentive listening
- Avoidance of pejorative and prejudicial terms
- Empathic attitude
- Written information to take away and read
- Encouragement to return with list of questions

The educational process may include answering questions about the natural history of the infection. The likely impact of the disease on the patient and how well they are coping should be assessed. Psychological issues and concerns can start to be addressed at the first session. Many patients will be worried about the risk of having acquired HIV or STIs, whether they are seen to be promiscuous, and about the doctor's opinion of them. The emotional consequences and perceived social stigma need to be addressed. The diagnosis of genital HPV may provoke a shock reaction and cause feelings such as guilt, anger, confusion and a sense of isolation.^{92,93}

Patients with genital HPV are usually very concerned about the diagnosis of the disease, its potential impact on their lives and how their family and friends will view them. Common concerns of patients relate to having an STI, transmitting the infection, fear of telling potential sexual partners who may then reject them and how it will affect their sex life and their social activities.^{87,92,93} Patients can be reassured that they are not alone in having genital HPV. It is important to provide accurate written information.⁹³

KEY INFORMATION FOR PATIENTS

- **Genital HPV (Human Papilloma Virus, more commonly known as wart virus) is a common virus that is carried by a large percentage of sexually active people.**
- **Not everyone who is infected with HPV will develop genital warts. This depends on their local immunity. Because HPV is such a common infection, genital warts are also very common.**
Most HPV infections do not show any symptoms so most people do not know when they are infected.
- **Getting visible genital warts in a long-term monogamous relationship does not mean the other partner has been unfaithful. It's possible that one or even both were exposed to the virus months or years previously and have carried it in a latent form (invisibly) without showing any symptoms.**
- **Most genital warts will disappear on their own.**
Genital warts can take some time to disappear, may cause discomfort and are unpleasant to have in such a vulnerable part of your body. There are a variety of treatments available to remove the warty lumps, but they do not necessarily get rid of the underlying virus infection.
- **After successful treatment, new crops of genital warts may recur – this usually happens for about one in three people.**
- **Most HPV infections appear to be efficiently cleared or suppressed by the body's immune system. But it is not known if HPV is completely cleared or remains without symptoms, invisible to the eye.**
- **After the warts have resolved, some experts believe that your ability to transmit HPV decreases after 18-24 months.**
Currently there is no test available to detect whether clearance of HPV has occurred.
- **Condoms may reduce the risk of transmission and should be used with new sexual partners. Introducing condoms into a long-term relationship is more debatable because your partner is probably already infected.**
- **Genital warts do not stop you having children.**
- **Genital warts do not stop you having sex.**
- **There is a link between certain types of genital HPV infection and cervical cancer. Women should have regular cervical smears as per the cervical screening programme to detect any early changes which can be monitored and/or treated, thereby preventing their progression to cancer.**
- **The HPV types that cause external visible warts are rarely associated with abnormalities on the cervix that can cause cancer.**

GUIDELINES ON THE MANAGEMENT OF ANOGENITAL HPV IN CHILDHOOD

Epidemiology

Following a dramatic increase between 1966 and 1984, HPV is now the most common viral infection of the adult and adolescent female genital tract.^{11,94} There are still no long term natural history studies of anogenital HPV infection in childhood. However, over the same period there was a parallel increase in the number of case reports of anogenital warts in children, which probably reflects a true increase in the childhood prevalence.⁹⁵⁻⁹⁷

Clinical behaviour

HPV infection of the ano-genital region is commonly asymptomatic. Children often present because a caregiver has noted the lesions, although some present with pain or bleeding on defaecation, or secondary infection. Classical cauliflower-like condyloma acuminata do occur in children, but anogenital warts have multiple appearances.^{98,99}

Many adults have disease at several levels of the genito-urinary tract.¹⁰⁰ Multi-centric disease has rarely been described in children, but it has seldom been looked for.¹⁰¹

The incubation period of ano-genital warts in adults is widely variable.¹ The incubation period in children is unknown, largely due to the uncertainties surrounding vertical transmission. There is a high likelihood of spontaneous regression over time.¹⁰² HPV may be particularly troublesome in children on immuno-suppressive therapy, and the possibility of immune deficiency (including HIV) should be considered in any child who has particularly refractory lesions.^{103,104}

Virology

Virologic diagnosis relies on the detection of HPV DNA (see page 8). The use of PCR has greatly increased sensitivity, but there is always a risk of contamination. Many HPV types have been described, but no specific type is invariably associated with a particular clinical appearance.¹⁰⁵ Infection with multiple types is common¹⁰⁶ and it is technically impossible to be sure that all types from a given patient have been isolated. HPV DNA can be found in apparently normal tissue surrounding clinical lesions¹⁰² and in vaginal washings from patients with no detectable lesions.^{100,107} In adolescents and adults, types 1-4 and 7 are found almost exclusively in skin warts.¹⁰⁵ In children however, there is a significant prevalence of types 1-3 in anogenital warts.^{108,109} Laryngeal papillomas are usually associated with HPV type 6 or 11.⁷⁹

In determining the source of infection, the virology adds little to the history and clinical examination.¹¹⁰ There is little if any value in typing for forensic purposes.

Neoplasia

In sexually active adolescents and adults, as has already been described, there is a striking association between HPV and dysplasia or carcinoma of the cervix, vulva, penis and anus. Malignancy has been reported in children with laryngeal papillomatosis.¹¹¹ The risk of late malignancy in children with anogenital infection is not known. There are case reports of vulval dysplasia and carcinoma in young adolescents who had vulval warts from infancy^{112,113} and of Bowenoid papulosis (intra-epithelial neoplasia) in childhood.^{114,115}

Methods of transmission in childhood

In adults, genital HPV is a sexually transmitted infection. Sexual transmission clearly occurs in children, but other forms of transmission also occur.

Sexual transmission: Adolescent genital HPV is associated with high risk sexual behaviour and early age at first intercourse,^{61,116} but is less likely to persist than infection in women who acquire it at an older age.^{61,117}

It was not recognised that anogenital warts in children might be sexually transmitted until 1971. From 1971 to 1993, 300 cases were published, of which 29% were sexually transmitted. The percentage of sexual abuse in various studies varies from 0-100%, which may reflect differences either in the populations studied or in the methodology.⁹⁸ Sexual abuse has been documented in infants whose warts presented as early as the first year of life,¹¹⁸ and suggested in some cases of oral or laryngeal papilloma. However, accumulating evidence suggests that the presence of warts in the anogenital region or oropharynx and/or the detection of HPV DNA in the anogenital region is not, in isolation, a reliable indicator of childhood sexual abuse.^{8,2,119-123}

Vertical transmission: HPV can be transferred from mothers to their offspring, probably from an infected birth canal.⁸² It is difficult to quantify the risk to these babies, but it appears low.^{83,124} There is no correlation between the presence of HPV DNA in the baby and the presence or absence of known clinical or virologic infection in the mother. The duration of viral shedding and/or persistence of HPV DNA on the skin of infected babies remains unclear. Although some authors have reported persistence of HPV DNA to two years of age,^{95,125} another longitudinal cohort study found almost no evidence of persistent perinatally acquired infection.¹²⁴

Vertically-transmitted HPV may also cause juvenile onset respiratory papillomatosis (laryngeal papillomas) that may present as hoarseness, or rarely as recurrent pneumonia or breathing difficulties due to lower respiratory tract involvement.⁷⁹ The upper limits of the incubation period from birth to clinical infection have not been established, but in laryngeal disease may be as long as five years.¹²²

Given that symptom-free infection is common in pregnancy (see above), one cannot completely exclude the possibility of vertical transmission in any child. However, one should remember that maternal infection does not prove vertical transmission. Several cases have been described in which the mother's sexual partner was abusing the child.^{126,127} On the basis of the evidence to date, it is reasonable to conclude that most vertical transmission will manifest itself in young children. It has therefore been suggested that child sexual abuse is not the most likely cause of HPV in the majority of cases involving children under the age of four years.¹²²

Other means of transmission: Dermatological literature suggests that children may acquire anogenital warts by infection from cutaneous warts on their own hands (auto-inoculation), or on the hands of adults (hetero-inoculation). Arguments for this hypothesis are the prevalence of HPV 2 in anogenital warts in childhood, and a number of suggestive case reports and case series.^{97,109,128} Although difficult to prove, some authors have also raised the possibility of fomite transmission.¹²³

In conclusion, it must be recognised that methods of transmission other than sexual contact do occur. The most common of these may be vertical transmission. However, this can never be assumed to be the case, and suggestions of auto-inoculation or innocent hetero-inoculation should always be regarded with caution. Sexual contact must be included in the differential diagnosis whenever a child or young person presents with anogenital warts.

Assessment

Establish the age at which the lesions first appeared, and what symptoms they cause. Consider all means of transmission: vertical (maternal infection including cervical smears; symptoms of respiratory infection); sexual transmission (adolescent sexual activity; disclosure of sexual abuse; behaviour changes; risk factors for sexual abuse such as contact with a known sexual offender or a family history of sexual abuse); other (other warts in the child or young person; warts in other relatives or caregivers).

Do not forget to examine the whole body (including the conjunctivae, mouth and throat) for warts. Examine the genitalia and anus with a light source and some kind of magnification, such as an auroscope. In females, part the labia and inspect the vulva carefully. In males, do not forget to examine the corona and frenum of the penis (if the foreskin is readily retractile). Not everything that presents as a wart is HPV. The most common alternative diagnosis is molluscum contagiosum, but almost any kind of papular rash may present in the ano-genital region. If there is doubt, the lesion may need to be biopsied, and tissue sent both for histology and for virological analysis.

Unless there is clear evidence of vertical transmission in an infant, auto-inoculation in a child or consenting sexual activity in an adolescent, consider referring the patient for a multi-disciplinary assessment for possible sexual abuse. If in doubt, consult with a paediatrician with expertise in this area. If you do refer, leave other investigations for sexual abuse to the doctor to whom you are referring. A full assessment for possible sexual abuse will include an examination by a doctor trained in the medical assessment of sexual abuse, a full screen for other STI following accepted forensic procedures, a social work assessment and a diagnostic interview by an appropriately trained interviewer. In many cases, the result will be inconclusive.¹²⁹

More extensive medical investigations may be needed if there are oral lesions or respiratory symptoms in a young child, or if lesions appear to extend into the anus, urethra or vagina. These might include laryngoscopy, proctoscopy, cystoscopy, vaginoscopy or (in post-pubertal girls) a speculum examination and cervical smear.

Treatment

Anogenital warts will usually regress spontaneously. Infection may be multi-focal, and HPV DNA is almost certainly present in adjacent 'normal' tissue. At present, there is no evidence that treatment in childhood will reduce the (unproven) risk of later neoplasia. Treatment "can be difficult, prolonged and only marginally efficacious"⁹⁴ and recurrence is common. For all these reasons, active treatment is not usually recommended. Treatment should be reserved for those with significant symptoms. There are many forms of treatment,¹²³ but in young children with extensive lesions, diathermy under general anaesthetic is probably the best option. Several case reports attest to the safety and efficacy of Podofilox gel (podophyllotoxin) or imiquimod cream in children.¹³⁰ However, there are no randomised controlled trials of therapy in childhood. The most common therapy for juvenile onset respiratory papillomatosis is laryngoscopy and surgical debulking with laser. The use of intralesional Cidofovir is under investigation.¹³¹

Follow-up

Follow the patient to ensure that the lesions regress, and see them again after three to six months to ensure that they have not recurred. In the case of vertical transmission, it is important to ensure that the mother receives appropriate follow-up of her own infection. If the patient is a sexually active adolescent, you should screen for other STIs and provide sexual health advice. In the case of sexual abuse, the patient should be followed to ensure that appropriate steps have been taken to ensure his or her ongoing safety and to provide support and counselling.

There is no evidence available to guide recommendations for long-term follow-up. It is reasonable to be concerned that children and adolescents with anogenital HPV infection may be at increased long-term risk of malignancy. It would therefore be reasonable to recommend early consultation by patients of either sex for ano-genital or urethral symptoms. Routine cervical screening should follow the National Cervical Screening Guidelines.

NOTES

CLINICAL PRESENTATIONS OF GENITAL HPV



Multifocal pigmented VIN



Penile pearly papules



Multifocal VIN



Penile warts



Vulval condyloma



Squamous cell carcinoma in situ of glans penis with early invasive carcinoma

References

1. Burchell AN, et al. Chapter 6: Epidemiology and transmission dynamics of genital HPV infection. *Vaccine*. 2006; 24 (Suppl 3):S52-S61.
2. Trottier H, et al. The epidemiology of genital human papillomavirus infection. *Vaccine*. 2006 Mar 30; 24 (Suppl 1):S1-15.
3. Partridge JM, Koutsky LA. Genital human papillomavirus infection in men. *The Lancet Infectious Diseases*. 2006 Jan; 6(1):21-31.
4. Collins SJ, et al. Proximity of first intercourse to menarche and the risk of human papillomavirus infection: a longitudinal study. *Int J Cancer*. 2005 Apr 10; 114(3):498-500.
5. Winer RL, et al. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. [see comment] [erratum appears in *Am J Epidemiol*. 2003 May 1; 157(9):858]. *Am J Epidemiol*. 2003 Feb 1; 157(3):218-26.
6. Brown DR, et al. Detection of multiple human papillomavirus types in Condylomata acuminata lesions from otherwise healthy and immunosuppressed patients. *J Clin Microbiol*. 1999 Oct; 37(10):3316-22.
7. Vandepapeliere P, et al. Randomized controlled trial of an adjuvanted human papillomavirus (HPV) type 6 L2E7 vaccine: infection of external anogenital warts with multiple HPV types and failure of therapeutic vaccination. *J Infect Dis*. 2005 Dec 15; 192(12):2099-107.
8. Wiley DJ, et al. External genital warts: diagnosis, treatment, and prevention. *Clin Infect Dis*. 2002 Oct 15; 35(Suppl 2):S210-24.
9. Gissmann L, et al. Human papillomavirus types 6 and 11 DNA sequences in genital and laryngeal papillomas and in some cervical cancers. *Proc Natl Acad Sci USA*. 1983 Jan; 80(2):560-3.
10. Habel LA, et al. Risk factors for incident and recurrent condylomata acuminata among women. A population-based study. *Sex Transm Dis*. 1998 Jul; 25(6):285-92.
11. Koutsky L. Epidemiology of genital human papillomavirus infection. *Am J Med*. 1997 May 5; 102(5A):3-8.
12. Schofield MJ, et al. Sexually transmitted infections and use of sexual health services among young Australian women: women's health Australia study. *Int J STD AIDS*. 2000 May; 11(5):313-23.
13. Dickson N, et al. The lifetime occurrence of sexually transmitted diseases among a cohort aged 21. *NZ Med J*. 1996 Aug 23; 109(1028):308-12.
14. Dickson N. Private Communication. 2006.
15. Baseman JG, Koutsky LA. The epidemiology of human papillomavirus infections. *J Clin Virol*. 2005 Mar; 32 (Suppl 1):S16-24.
16. Van Den Eeden SK, et al. Risk factors for incident and recurrent condylomata acuminata among men. A population-based study. *Sex Transm Dis*. 1998 Jul; 25(6):278-84.
17. Manhart LE, et al. Human papillomavirus infection among sexually active young women in the United States: Implications for developing a vaccination strategy. [see comment]. *Sex Transm Dis*. 2006 Aug; 33(8):502-8.
18. Brisson J, et al. Condyloma and intraepithelial neoplasia of the uterine cervix: a case-control study. [see comment]. *Am J Epidemiol*. 1988 Aug; 128(2):337-42.
19. Wheeler CM, et al. Determinants of genital human papillomavirus infection among cytologically normal women attending the University of New Mexico student health center. *Sex Transm Dis*. 1993 Sep-Oct; 20(5):286-9.
20. Hildesheim A, et al. Determinants of genital human papillomavirus infection in low-income women in Washington, D.C. *Sex Transm Dis*. 1993 Sep-Oct; 20(5): 279-85.
21. Seshadri L, et al. Cervical intraepithelial neoplasia and human papilloma virus infection in renal transplant recipients. *Indian J Cancer*. 2001 Jun-Dec; 38(2-4):92-5.
22. Oriel JD. Natural history of genital warts. *Br J Vener Dis*. 1971 Feb; 47(1):1-13.
23. Barnabas RV, et al. Epidemiology of HPV 16 and cervical cancer in Finland and the potential impact of vaccination: mathematical modelling analyses. [see comment]. *PLoS Medicine/Public Library of Science*. 2006 May; 3(5):e138.
24. Beutner KR, et al. Human papillomavirus and human disease. *Am J Med*. 1997 May 5; 102(5A):9-15.
25. Manhart LE, Koutsky LA. Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis. *Sex Transm Dis*. 2002 Nov; 29(11):725-35.
26. Winer RL, et al. Condom use and the risk of genital human papillomavirus infection in young women. [see comment]. *N Engl J Med*. 2006 Jun 22; 354(25):2645-54.
27. Munoz N, et al. Chapter 1: HPV in the etiology of human cancer. *Vaccine*. 2006; 24(Suppl 3):S1-S10.
28. Beral V. Cancer of the cervix: a sexually transmitted infection? *Lancet*. 1974 May 25; 1(7865):1037-40.
29. IARC. IARC monographs on the evaluation of carcinogenic risks to humans. Human Papillomaviruses, vol. 64. Lyon: International Agency for Research on Cancer 1995.
30. Walboomers JM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. [see comment]. *J Pathol*. 1999 Sep; 189(1):12-9.
31. Bosch FX, et al. The causal relation between human papillomavirus and cervical cancer. [see comment]. *J Clin Pathol*. 2002 Apr; 55(4):244-65.
32. IARC. Monographs on the evaluation of carcinogenic risks to humans. Human Papillomaviruses, vol. 90. Lyons: International Agency for Research on Cancer In Press.
33. Clifford G, et al. Chapter 3: HPV type-distribution in women with and without cervical neoplastic diseases. *Vaccine*. 2006; 24(Suppl 3):S26-S34.
34. Moscicki A-B, et al. Chapter 5: Updating the natural history of HPV and anogenital cancer. *Vaccine*. 2006; 24(Suppl 3): S42-S51.
35. Khan MJ, et al. The elevated 10-year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice. *J Natl Cancer Inst*. 2005 Jul 20; 97(14):1072-9.
36. Lorincz AT, et al. Viral load of human papillomavirus and risk of CIN3 or cervical cancer. *Lancet*. 2002 Jul 20; 360(9328):228-9.
37. Schiffman M, et al. The carcinogenicity of human papillomavirus types reflects viral evolution. *Virology*. 2005 Jun 20; 337(1):76-84.
38. Winer RL, et al. Development and duration of human papillomavirus lesions, after initial infection. *J Infect Dis*. 2005 Mar 1; 191(5):731-8.
39. Carcinoma of the cervix and tobacco smoking: Collaborative reanalysis of individual data on 13,541 women with carcinoma of the cervix and 23,017 women without carcinoma of the cervix from 23 epidemiological studies. *Int J Cancer*. 2006 Mar 15; 118(6):1481-95.
40. McIntyre-Seltman K, et al. Smoking is a risk factor for cervical intraepithelial neoplasia grade 3 among oncogenic human papillomavirus DNA-positive women with equivocal or mildly abnormal cytology. *Cancer Epidemiol Biomarkers Prev*. 2005 May; 14(5):1165-70.
41. Cogliano V, et al. Carcinogenicity of combined oestrogen-progestagen contraceptives and menopausal treatment. [see comment]. *Lancet Oncology*. 2005 Aug; 6(8):552-3.
42. International Collaboration of Epidemiological Studies of Cervical C, International Collaboration of Epidemiological Studies of Cervical C. Cervical carcinoma and reproductive factors: collaborative reanalysis of individual data on 16,563 women with cervical carcinoma and 33,542 women without cervical carcinoma from 25 epidemiological studies. *Int J Cancer*. 2006 Sep 1; 119(5):1108-24.

43. Smith JS, et al. Chlamydia trachomatis and invasive cervical cancer: a pooled analysis of the IARC multicentric case-control study. *Int J Cancer*. 2004 Sep 1; 111(3):431-9.
44. Koutsky LA, et al. A controlled trial of a human papillomavirus type 16 vaccine. [see comment]. *N Engl J Med*. 2002 Nov 21; 347(21):1645-51.
45. Mao C, et al. Efficacy of human papillomavirus-16 vaccine to prevent cervical intraepithelial neoplasia: a randomized controlled trial. [see comment]. *Obstet Gynecol*. 2006 Jan; 107(1):18-27.
46. Villa LL, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. [see comment]. *Lancet Oncology*. 2005 May; 6(5):271-8.
47. Ferris D/FISG. Efficacy of a quadrivalent HPV (types 6/11/16/18) L1 virus-like particle (VLP) vaccine in women with virologic evidence of HPV infection: A combined analysis. Eurogin Conference 2006; Paris, 2006.
48. Ferris D. For the Future II Study Group. Efficacy of a quadrivalent HPV (types 6/11/16/18) L1 virus-like particle (VLP) vaccine in women with virologic evidence of HPV infection: A combined analysis. Eurogin Conference 2006; Paris, 2006.
49. Harper DM, et al. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. *Lancet*. 2006 Apr 15; 367(9518):1247-55.
50. Harper DM, et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. [see comment]. *Lancet*. 2004 Nov 13-19; 364(9447):1757-65.
51. Koutsky LA, Harper DM. Chapter 13: Current findings from prophylactic HPV vaccine trials. *Vaccine*. 2006; 24(Suppl 3): S114-S21.
52. Stanley M, et al. Chapter 12: Prophylactic HPV vaccines: Underlying mechanisms. *Vaccine*. 2006; 24(Suppl 3): S106-S13.
53. Burkhart CG, Burkhart CG. The endogenous, exogenous, and latent infections with human papillomavirus. *Int J Dermatology*. 2004 Jul; 43(7):548-9.
54. Sterling J. Anogenital warts. In: Burns T, Breathnach S, Cox N, Griffiths C eds. *Rook's Textbook of Dermatology*: Blackwell Publishing 2004:45-7.
55. Bunker CB, Neill SM Male genital dermatology. In: Burns T, Breathnach S, Cox N, Griffiths C eds. Blackwell Publishing 2004:32.
56. Bunker CB, Neill SM Female genital dermatology. In: Burns T, Breathnach S, Cox N, Griffiths C eds. Blackwell Publishing 2004:70.
57. Sterling J. Vulval intraepithelial neoplasia, penile intraepithelial neoplasia and Bowenoid papulosis. In: Burns T, Breathnach S, Cox N, Griffiths C eds. Blackwell Publishing 2004:55-6.
58. Bunker CB Neill SM Vulval intraepithelial neoplasia. In: Burns T, Breathnach S, Cox N, Griffiths C eds. Blackwell Publishing 2004:74-6.
59. Bunker CB Neill SM Erythroplasia of Queyrat, Bowen's disease of the penis and bowenoid papulosis. In: Burns T, Breathnach S, Cox N, Griffiths C eds. Blackwell Publishing 2004:35-6.
60. Snijders PJ, et al. The clinical relevance of human papillomavirus testing: relationship between analytical and clinical sensitivity. *J Pathol*. 2003 Sep; 201(1):1-6.
61. von Krogh G, et al. European guideline for the management of anogenital warts. *Int J STD AIDS*. 2001 Oct; 12 (Suppl 3):40-7.
62. Ho GY, et al. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med*. 1998 Feb 12; 338(7):423-8.
63. Wilson J, Wilson J. Treatment of genital warts – what's the evidence? *Int J STD AIDS*. 2002 Apr; 13(4):216-20; quiz 21-2.
64. Coleman N, et al. Immunological events in regressing genital warts. *Am J Clin Pathol*. 1994 Dec; 102(6):768-74.
65. Berman B, et al. Determination of the area of skin capable of being covered by the application of 250 mg of 5% imiquimod cream. *Dermatol Surg*. 2004 May; 30(5):784-6.
66. Garland SM, et al. An open-label phase II pilot study investigating the optimal duration of imiquimod 5% cream for the treatment of external genital warts in women. *Int J STD AIDS*. 2006 Jul; 17(7):448-52.
67. Brockmeyer NH, et al. Treatment of condylomata acuminata with pegylated interferon alfa-2b in HIV-infected patients. *Eur J Med Res*. 2006 Jan 31; 11(1):27-32.
68. Orlando G, et al. Combined surgery and cidofovir is an effective treatment for genital warts in HIV-infected patients. *AIDS*. 2002 Feb 15; 16(3):447-50.
69. Herzinger T, et al. Photodynamic therapy of genital condylomata in men. *Clin Exp Dermatol*. 2006 Jan; 31(1):51-3.
70. Wang XL, et al. Topical 5-aminolaevulinic acid-photodynamic therapy for the treatment of urethral condylomata acuminata. *Br J Dermatol*. 2004 Oct; 151(4):880-5.
71. Zaak D, et al. Recurrence of condylomata acuminata of the urethra after conventional and fluorescence-controlled Nd:YAG laser treatment. *Urology*. 2003 May; 61(5):1011-5.
72. Yu X, et al. [Efficacy of local injection of bacillus calmette-guerin polysaccharide nucleic acid following CO2 laser resection on condyloma acuminatum]. *Zhong Hua Nan Ke Xue*. 2004 Feb; 10(2):117-8.
73. Metawea B, et al. Application of viable bacille Calmette-Guerin topically as a potential therapeutic modality in condylomata acuminata: a placebo-controlled study. *Urology*. 2005 Feb; 65(2):247-50.
74. Tsambaos D, et al. Treatment of condylomata acuminata with oral isotretinoin. *J Urol*. 1997 Nov; 158(5):1810-2.
75. Gunter J. Genital and perianal warts: new treatment opportunities for human papillomavirus infection. *Am J Obstet Gynecol*. 2003 Sep; 189(Suppl 3):S3-11.
76. Schultz RE, et al. Clinical and molecular evaluation of acetowhite genital lesions in men. *J Urol*. 1990 May; 143(5):920-3.
77. Bergman A, et al. Prevalence of human papillomavirus infection in men. Comparison of the partners of infected and uninfected women. *J Reprod Med*. 1992 Aug; 37(8):710-2.
78. O'Hanlan KA, et al. Human papillomavirus-associated cervical intraepithelial neoplasia following lesbian sex. *Obstet Gynecol*. 1996 Oct; 88(4 Pt 2):702-3.
79. Beutner KR, et al. Genital warts and their treatment. *Clin Infect Dis*. 1999 Jan; 28(Suppl 1):S37-56.
80. Silverberg MJ, et al. Condyloma in pregnancy is strongly predictive of juvenile-onset recurrent respiratory papillomatosis. *Obstet Gynecol*. 2003 Apr; 101(4):645-52.
81. Tasca RA, et al. Recurrent respiratory papillomatosis. *Arch Dis Child*. 2006 Aug; 91(8):689-91.
82. Mandelbrot L. Vertical transmission of viral infections. *Curr Opin Obstet Gynecol*. 1998 Apr; 10(2):123-8.
83. Jayasinghe Y, et al. Genital warts in children: what do they mean? *Arch Dis Child*. 2006 Aug; 91(8):696-700.
84. Smith EM, et al. Human papillomavirus prevalence and types in newborns and parents: concordance and modes of transmission. [see comment]. *Sex Transm Dis*. 2004 Jan; 31(1):57-62.
85. Winer RL, et al. Delivering reassurance to parents: perinatal human papillomavirus transmission is rare.[comment]. *Sex Transm Dis*. 2004 Jan; 31(1):63-4.
86. Medeiros LR, et al. Vertical transmission of the human papillomavirus: a systematic quantitative review. *Cad Saude Publica*. 2005 Jul-Aug; 21(4):1006-15.
87. Einarson A, et al. The use of topical 5% imiquimod during pregnancy: a case series. *Reprod Toxicol*. 2006 Jan; 21(1):1-2.

88. Warren T, et al. Counseling the patient who has genital herpes or genital human papillomavirus infection. *Infect Dis Clin North Am*. 2005 Jun; 19(2):459-76.
89. Reitano M. Counseling patients with genital warts. *Am J Med*. 1997 May 5; 102(5A):38-43.
90. Fortenberry JD. Health care seeking behaviors related to sexually transmitted diseases among adolescents. *Am J Public Health*. 1997 Mar; 87(3):417-20.
91. Fortenberry JD, et al. Relationships of stigma and shame to gonorrhea and HIV screening. *Am J Public Health*. 2002 Mar; 92(3):378-81.
92. Sankar P, et al. To tell or not to tell: primary care patients' disclosure deliberations. *Arch Intern Med*. 2005 Nov 14; 165(20):2378-83.
93. McCaffery K, et al. Testing positive for human papillomavirus in routine cervical screening: examination of psychosocial impact. [erratum appears in *BJOG*. 2004 Dec; 111(12):1489]. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2004 Dec; 111(12):1437-43.
94. McCaffery K, et al. Social and psychological impact of HPV testing in cervical screening: a qualitative study. *Sex Transm Infect*. 2006 Apr; 82(2):169-74.
95. Centers for Disease C, Centers for Disease C. Condyloma acuminatum – United States, 1966-1981. *MMWR – Morbidity & Mortality Weekly Report*. 1983 Jun 17; 32(23):306-8.
96. Rice PS, et al. High prevalence of human papillomavirus type 16 infection among children. *J Med Virol*. 2000 May; 61(1):70-5.
97. Oriol JD. Sexually transmitted diseases in children: human papillomavirus infection. *Genitourin Med*. 1992 Apr; 68(2):80-3.
98. Cohen BA, et al. Anogenital warts in children. Clinical and virologic evaluation for sexual abuse. [see comment]. *Arch Dermatol*. 1990 Dec; 126(12):1575-80.
99. Boyd AS. Condylomata acuminata in the pediatric population. [see comment]. *Am J Dis Child*. 1990 Jul; 144(7):817-24.
100. Moscicki AB. Genital HPV infections in children and adolescents. *Obstet Gynecol Clin North Am*. 1996 Sep; 23(3):675-97.
101. Spitzer M, et al. The multicentric nature of disease related to human papillomavirus infection of the female lower genital tract. *Obstet Gynecol*. 1989 Mar; 73(3 Pt 1):303-7.
102. Gutman LT, et al. Evaluation of sexually abused and nonabused young girls for intravaginal human papillomavirus infection. *Am J Dis Child*. 1992 Jun; 146(6):694-9.
103. Allen AL, et al. The natural history of condyloma in children. *J Am Acad Dermatol*. 1998 Dec; 39(6):951-5.
104. Cripe TP. Human papillomaviruses: pediatric perspectives on a family of multifaceted tumorigenic pathogens. [see comment]. *Pediatr Infect Dis J*. 1990 Nov; 9(11):836-44.
105. Formar AB, et al. Association of human immunodeficiency virus seropositivity and extensive perineal condylomata acuminata in a child. *Arch Dermatol*. 1988 Jul; 124(7):1010-1.
106. Padel AF, et al. Human papillomaviruses in anogenital warts in children: typing by in situ hybridisation. [see comment]. *BMJ*. 1990 Jun 9; 300(6738):1491-4.
107. Davis AJ, et al. Human papilloma virus infection in the pediatric and adolescent patient. [see comment]. *J Pediatr*. 1989 Jul; 115(1):1-9.
108. Stevens-Simon C, et al. The prevalence of genital human papillomavirus infections in abused and nonabused preadolescent girls. *Pediatrics*. 2000 Oct; 106(4):645-9.
109. Raimer SS, et al. Family violence, child abuse, and anogenital warts. *Arch Dermatol*. 1992 Jun; 128(6):842-4.
110. Handley J, et al. Common association of HPV 2 with anogenital warts in prepubertal children. *Pediatr Dermatol*. 1997 Sep-Oct; 14(5):339-43.
111. Siegfried EC, et al. Anogenital warts in children. *Adv Dermatol*. 1997; 12:141-66; discussion 67.
112. Bennett RS, et al. Human papillomaviruses: associations between laryngeal papillomas and genital warts. *Pediatr Infect Dis J*. 1987 Mar; 6(3):229-32.
113. Boutselis JG. Intraepithelial carcinoma of the vulva. *Am J Obstet Gynecol*. 1972 Jul 15; 113(6):733-8.
114. Lister UM, et al. Carcinoma of the vulva in childhood. *J Obstet Gynaecol Br Commonw*. 1972 May; 79(5):470-3.
115. Godfrey JC, et al. Successful treatment of bowenoid papulosis in a 9-year-old girl with vertically acquired human immunodeficiency virus. *Pediatrics*. 2003 Jul; 112(1 Pt 1):e73-6.
116. Breneman DL, et al. Bowenoid papulosis of the genitalia associated with human papillomavirus DNA type 16 in an infant with atopic dermatitis. *Pediatr Dermatol*. 1985 Jul; 2(4):297-301.
117. Kahn JA, et al. Mediators of the association between age of first sexual intercourse and subsequent human papillomavirus infection. *Pediatrics*. 2002 Jan; 109(1):E5.
118. Moscicki AB, et al. The natural history of human papillomavirus infection as measured by repeated DNA testing in adolescent and young women. *J Pediatr*. 1998 Feb; 132(2):277-84.
119. McCoy CR, et al. Condyloma acuminata: an unusual presentation of child abuse. *J Pediatr Surg*. 1982 Oct; 17(5):505-7.
120. Myhre AK, et al. Anogenital human papillomavirus in non-abused preschool children. *Acta Paediatr*. 2003 Dec; 92(12):1445-52.
121. Powell J, et al. Genital carriage of human papilloma virus (HPV) DNA in prepubertal girls with and without vulval disease. *Pediatr Dermatol*. 2003 May-Jun; 20(3):191-4.
122. Mant C, et al. Buccal exposure to human papillomavirus type 16 is a common yet transitory event of childhood. *J Med Virol*. 2003 Dec; 71(4):593-8.
123. Sinclair KA, et al. Anogenital and respiratory tract human papillomavirus infections among children: age, gender, and potential transmission through sexual abuse. *Pediatrics*. 2005 Oct; 116(4):815-25.
124. Sinal SH, et al. Human papillomavirus infections of the genital and respiratory tracts in young children. *Seminars in Pediatric Infectious Diseases*. 2005 Oct; 16(4):306-16.
125. Watts DH, et al. Low risk of perinatal transmission of human papillomavirus: results from a prospective cohort study. [see comment]. *Am J Obstet Gynecol*. 1998 Feb; 178(2):365-73.
126. Rintala MA, et al. Transmission of high-risk human papillomavirus (HPV) between parents and infant: a prospective study of HPV in families in Finland. *J Clin Microbiol*. 2005 Jan; 43(1):376-81.
127. Hanson RM, et al. Anogenital warts in childhood. [see comment]. *Child Abuse Negl*. 1989; 13(2):225-33.
128. Herman-Giddens ME, et al. Association of coexisting vaginal infections and multiple abusers in female children with genital warts. *Sex Transm Dis*. 1988 Jan-Mar; 15(1):63-7.
129. Obalek S, et al. Condylomata acuminata in children: frequent association with human papillomaviruses responsible for cutaneous warts. *J Am Acad Dermatol*. 1990 Aug; 23(2 Pt 1):205-13.
130. Kelly P, et al. Sexually transmitted infections in alleged sexual abuse of children and adolescents. *J Paediatr Child Health*. 2006 Jul-Aug; 42(7-8):434-40.
131. Majewski S, et al. Imiquimod is highly effective for extensive, hyperproliferative condyloma in children. *Pediatr Dermatol*. 2003 Sep-Oct; 20(5):440-2.
132. Kimberlin DW, et al. Juvenile onset recurrent respiratory papillomatosis: possibilities for successful antiviral therapy. *Antiviral Res*. 2000 Feb; 45(2):83-93.

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