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Genital warts and human papillomavirus: An update

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ABSTRACT

Genital warts are the visible manifestations of infection caused by human papillomavirus. They are commonly encountered in primary care health centers. The guidelines for treatment selection are limited. The main goal of treatment is clearance of visible warts and treatment reduces infectivity, but there is no evidence that treatment reduces the risk of cervical and genital cancer. Choice of therapy by the physician is based on the site, size, number and morphology of lesions, as well as patient preference for physician, treatment cost, convenience and adverse effect. Genital warts can cause significant emotional distress due to fear of social stigma and lesions can be of aesthetic concern. Genital warts can lead to cervical cancer which is ranked as the most frequent cancer of women in India. India has a population of approximately 365.71 million women above 15 years of age, who are at risk of developing cervical cancer. The current estimates indicate approximately 132,000 new cases diagnosed and 74,000 deaths annually in India, accounting to nearly 1/3 rd of the global cervical cancer deaths. Warts have been reported in 2-25% of sexually transmitted disease clinic attendees in India. Women with genital warts should have cervical smears examined as recommended by the national cervical screening program.

Keywords: Genital warts, human papillomavirus, cervical cancer, HPV vaccine.

INTRODUCTION

Genital warts are the infection caused by one or more types of 100 recognized human papillomaviruses (HPVs) [1]. Genital warts are one of the most common kinds of STDs (sexually transmitted diseases) or STIs (sexually transmitted infections) and also known as venereal warts or condylomata acuminate [2].

They are the visible manifestations and an important issue for women concerned about transmission of genital warts and human papillomavirus (HPV) to their sexual partners. Genital HPV is absent in the majority of women who have not had sexual intercourse' Although transmission is believed to be predominantly through sexual intercourse, studies have detected HPV DNA in cervical or vulva-vaginal samples from women who did not have sexual intercourse [3]. Transmission of HPV is enhanced when the superficial epithelium is disrupted as this is where the infectious agent resides [4, 5].

A study found that over 60% of people who have sexual relations with a person who has genital warts will become infected and develop them too. It is estimated 10% of young women in England have been infected with one or more strains of human papillomavirus by the age of 16. Another study found that 26% of US girls aged 14 to 19 have at least one sexually transmitted disease [6-8].

INDIAN SCENARIO OF CERVICAL CANCER, GENITAL WARTS AND HPV INFECTION

In India, cervical cancer ranks number one among cancer in females with an annual incidence of more than 132,000 new cases diagnosed and around 74000 deaths every year, accounting to nearly 1/3 rd of the global cervical cancer deaths [6]. India has a population of approximately 365.71 million women above 15 years of age, who are at risk of developing cervical cancer. Indian women face a 2.5% cumulative lifetime risk and 1.4% cumulative death risk from cervical cancer. At any given time, about 6.6% of women in the general population are estimated to harbor cervical HPV infection. HPV serotypes 16 and 18 account for nearly 76.7%\of cervical cancer in India. Warts have been reported in 2-25% of sexually transmitted disease clinic attendees in India; however, there is no data on the burden of anogenital warts in general community [9, 10].

THE HPV VIRUS AND TYPES

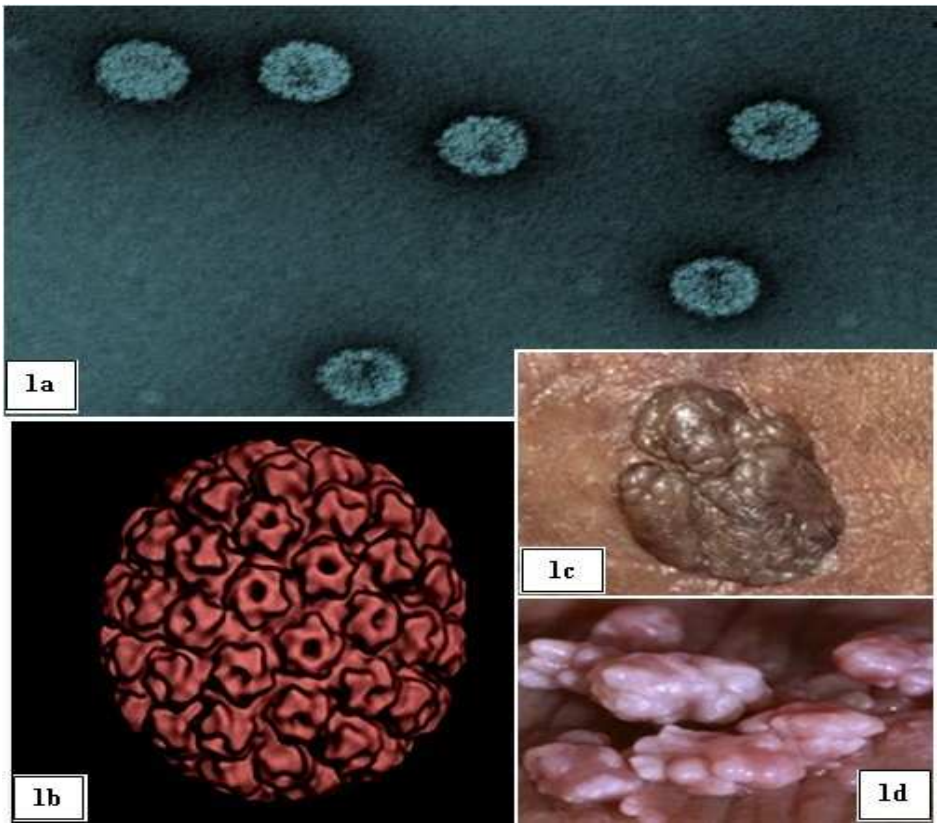

Fig.1, Images of human papillomavirus (1a, 1b) & genital warts (1c, 1d)

HPV is a member of the family Papillomaviridae (Figure 1a, 1b) [11]. They are deoxyribonucleic acid (DNA) viruses, non-enveloped and small in size [12]. Their classification is according to DNA sequence using the major (L1) and minor (L2) structural proteins. Only 15-20 are oncogenic out of over 100 serotypes of HPV which have been discovered. The lag period is 15-20 years between oncogenic HPV infection and the invasive cervical cancer. Genital HPVs are further grouped into high-risk types, probable high-risk types and low-risk types based on their association with cervical cancer. Worldwide, high-risk type HPV-16 and 18 contribute over 70% of all cervical cancer cases (the most prevalent being HPV-16 in at least 50-60% and HPV-18 in at least 10-12%), associated with anogenital and oropharyngeal cancers [13]. Similarly, in Indian women, the most common prevalent genotypes are HPV-16 and 18. Non-oncogenic HPV serotypes-6 and 11 contribute over 90% of benign genital infections such as genital warts (Figure 1c, 1d) and low-grade changes in cervical cells [14]. Other low-risk HPV types include HPV 40, 42, 43, 44, 54, 61, 70, 72, and 81[13] The high-risk types 16 and 18 are known to cause about 70% of all cases of invasive cervical cancer [15]. HPV 16 has the greatest oncogenic potential and continues to be the dominant oncogenic type worldwide. Other oncogenic HPV types including 31, 33, 35, 45, 52, and 58 are phylogenetically related to HPV 16/18 and account for an additional 18% of all cases [16]. In India, HPV 16, 18, 31, 33, and 45

account for more than 90% of cervical cancer cases [17]. Oncogenic HPV serotypes have also been implicated in the causation of anal, vulvar, vaginal, penile and oropharyngeal cancers [18].

The HPV life cycle begins with infection of basal cell layer of epithelium and progresses with epithelial cell differentiation, resulting in complete virions present in the epithelial cells in superficial layer. The greatest risk of transmission is likely to exist when genital warts are present, as they reflect a productive HPV infection [5].

There is also risk of transmission of HPV to offspring. The increasing frequency of childhood genital warts has been proposed to be the result of sexual abuse [6]. Non-sexual transmission of genital warts from mothers is also possible during passage through birth canal if mothers have external or cervical genital warts. Additional data supports a vertical (transplacental) transmission of HPV DNA, as over 50% of children born to HPV 16- or 18-infected mothers were positive for these HPVs [7].

PSYCHOLOGICAL ASPECTS OF GENITAL WARTS

Genital warts are associated with discomfort, pain, emotional stress and cosmetically unacceptable [19, 20]. The psychological stress of having genital warts is often greater than the medical effects of disease as reported. Some of the psychological outcomes of patients with genital HPV infection are a fear of cancer, impairments to their sex life and worsening of emotional relationship with their partner [8].

In an international survey of patients', it has been reported that 61% of women were 'quite' or 'very' concerned about having genital warts [21], with recurrence and transmission being the greatest concern. 95% of women believed that there was a risk associated with genital warts, the most common risks were link to cervical cancer or to an unspecified cancer. Approximately 40% of women believed that having genital warts had changed their lifestyles; particularly sexual behavior had changed, resulting in an increase in condom usage during sexual intercourse, abstinence from sexual intercourse, increased caution about new partners and a decrease in the number of sexual partners [2].

CAUSES OF GENITAL WARTS

Genital warts are caused by various types of human papillomavirus (HPV) that infect the top layers of skin. There are over 100 different types of HPV that may cause warts, but only a small number of strains can cause genital warts. Those that do cause genital warts are highly contagious and are passed on through sexual contact with a person who is infected. HPV types 6 and 11 cause the majority of genital warts [1, 22].

RISK FACTORS FOR GENITAL WARTS [23]

- Starting sexual relations at a young age
- Having sex with a person whose sexual history is unknown
- Having unprotected sex
- Having unprotected sex with many different people
- Having stress and other sexually transmitted disease (STD) at the same time
- Poor personal hygiene

COMPLICATIONS OF GENITAL WARTS

Cancer - HPV infection is closely associated with cervical cancer, as well as cancer of the vulva, anus and penis. The majority of cervical cancers are caused by HPV infection globally [24]. All HPV infections do not lead to cervical cancer but it is crucial for a woman's long-term health that she has regular Pap tests. Some HPV infections are also closely linked to oral, head and neck cancers as reported [25].

Pregnancy problems - pregnant women with genital warts may have problems urinating. Her vaginal tissues may stretch less during childbirth if there are warts on the vaginal wall. There is a very small risk that A mother with genital warts while giving birth may cause the baby to have warts in his/her throat (laryngeal papillomatosis) – if so happens surgery may be needed to prevent the airway from becoming obstructed. Hormonal changes during pregnancy may cause genital warts to grow, bleed, or increase in number [26, 27].

DIAGNOSIS OF GENITAL WARTS

Diagnosis of genital and anal warts is primarily clinical but typical leisions should be confirmed by histology [28]. The differential diagnosis includes benign or malignant neoplasm (e.g., squamous cell carcinoma in situ, Bowen's disease), molluscumcontagiosum (especially in patients with human immunodeficiency virus [HIV]), condylomalata, fibroepitheliomas, and pearly penile papules. Genital warts are flesh-colored, exophytic lesions on the external genitalia, including penis, scrotum, perineum, vulva and perianal skin. External warts can appear as small bumps, or they may be flat, verrucous, or pedunculated. Warts can also appear as reddish or brown smooth, raised papules (Figure 1c, 1d) or as dome-shaped lesions of 1 to 4 mm on keratinized skin [29, 30].

Diagnosis of genital warts by biopsy and viral typing is not recommended for patients with routine or typical lesions. Biopsy is required if the patient is immunocompromised, has a poor response to appropriate therapy and if the diagnosis is uncertain or has warts that are pigmented, indurated, fixed, or ulcerated, or is at high risk for HPV-related malignancy (e.g., chronic genital warts, tobacco use, history of abnormal Papanicolaou [Pap] smears) [1,30]. Oral sex raises the risk of genital warts developing in the mouth or throat, a patient needs to be examined by a health care professional to confirm diagnosis of genital warts [24, 31].

It is still possible to have genital warts even if a person's partner has no symptoms. People should go for a checkup if,

- The patient or partner has genital warts symptoms
- The patient recently had unprotected sex with a new partner
- The patient or partner have had unprotected sex with somebody else
- The patient's partner tells him/her that he/she has an STD
- The patient has an STD
- The patient is pregnant
- The patient is trying to get pregnant

A healthcare professional can usually diagnose genital warts if any are visible. The examination may involve looking inside the vagina or anus. On rare occasions a biopsy of the wart may be taken. Sometimes, even if no warts are detected, the doctor or nurse may ask the patient to come back at a later date. Visible warts may not appear straight after infection [30, 32-33].

APPEARANCE OF GENITAL WARTS

They may appear as flesh-colored or gray swellings (bumps) in the patient's genital area in and around the entrance to vagina or anus, on the cervix of uterus and on the penis, scrotum, groin or thigh (Figure 2a, 2b).

Fig.2 Severe case of genital warts on (2a) male and (2b) female

There may be a single wart or several clustered together to have a cauliflower shape.
They may be tiny, raised or flat, can be itchy or painless [23, 34-35].

TREATMENT AND CHOICE OF THERAPY FOR GENITAL WARTS

Genital warts, manifestations of common viral sexually transmitted diseases are diagnosed and treated with clinical specialists although treatment is not shown to reduce the transmission to sexual partners nor to prevent progression to dysplasia or cancer., Women with genital warts or those whose partners have genital warts should have a routine cervical cytological screening (Papanicolaou smear) to detect cervical dysplasia [36].

Patients with visible warts are only treated by doctors. The type of treatment depends on following information,

- Location of warts
- Number of warts
- Appearance of warts

Untreated visible genital warts may resolve spontaneously, remain the same, or increase in size. The main goal of treatment is removal of symptomatic warts but it may also reduce the persistence of HPV DNA in genital tissue, and therefore may reduce infectivity. However, there is currently no evidence that treatment of genital warts has a favorable impact on the incidence of cervical and genital cancer [37] and there have been no controlled studies on the effects of treatment of external genital warts and HPV transmission rates [38].

Choice of therapy by the physician is based on the site, size, number and morphology of lesions, as well as patient preference for physician, treatment cost, convenience and adverse effect. Routine follow-up for two to three months is advised to monitor response to therapy and for recurrence. Switching to a new treatment modality is appropriate if there is no response after three treatment cycles if the diagnosis is certain [39].

The main aim of treatment is getting rid of visible warts and lowering the number of viruses present. The patient's immune system has a better chance of fighting them off if the amount of viruses can be lowered. The following treatments are effective in getting rid of visible warts:

Topical medication - a cream or liquid is applied directly onto the warts for a few days each week. Treatment may continue for several weeks. This may be either administered by the patient at home or at a clinic depending on the kind of treatment.

Cryotherapy- liquid nitrogen is often used to freeze the warts, which causes a blister to form around the wart. As the skin heals, the lesions slide off, allowing new skin to appear. Sometimes repeated treatments are needed.

Electrocautery - the patient is generally given a local anesthetic and electric current is used to destroy the wart.
Surgery - the patient is given a local anesthetic and the wart will be cut out (excised).

Laser treatment - an intensive beam of light is used to destroy the wart.

Doctors may use more than one treatment at the same time. Although treatments are not painful, but may sometimes be uncomfortable, with some soreness and irritation for one or two days. Pain killers may be taken by the patients after treatment. A warm bath helps some patients who feel sore but make sure to dry the affected area completely after bath and use of bath oils, soap, creams, etc. should be avoided until the treatment is completed. Treatments available over-the-counter for ordinary warts (non genital warts) are not suitable for genital warts treatment [40-42].
The two methods of genital warts treatment can be chemical or ablative. The mechanism of action [43] and treatment cycles [30] are summarized in figure 3, Comparison of treatment for genital warts with adverse effects, response rates and recurrence rates are summarized in Table 1 [43-47]. The response rate for all treatments is approximately 60 to 90 percent [38-43].

CHEMICAL TREATMENTS

Patient-Applied

***Imiquimod (Aldara*)**

Imiquimod 5 percent cream is available in single use packets. It is a topical cell-mediated immune response modifier. A thin layer is applied to external visible warts by the patient and then rubbed until it vanishes. The area is washed with soap and water 6 to 10 hours after treatment. Sexual contact is not recommended while the cream is on the skin as imiquimod may weaken condoms and diaphragms [48].

Podofilox (Condylox)
Podofilox is purified extract of the most active compound of podophyllin available in 0.5 percent gel or solution. The solution should be applied with a cotton swab, gel should be applied with a finger. Some physicians prefer to perform the initial application. Patients should allow the solution to dry before moving around to prevent local irritation. Podofilox is not recommended for treatment of perianal, rectal, urethral, or vaginal lesions. Five randomized trials comparing podofilox with podophyllin found no difference in wart clearance rates [46].

Physician-Applied [38]
Podophyllin Resin
The standard treatment for genital warts is a 15 to 25 percent solution of podophyllin resin. Not more than 0.5 ml solution should be used and may not be applied to the cervix, vagina, or anal canal where the squamocolumnar junction is prone to dysplastic changes. The overall cost of treatment with podophyllin increases because it requires frequent office visits although it is inexpensive. The solution should be allowed to dry completely after application to prevent irritation. Some specialists recommend that the area of application be washed thoroughly one to four hours after application to reduce local irritation, although there is no evidence that doing so improves patient outcomes [49].

Trichloroacetic Acid
Few small, moist lesions can be treated with a solution of 60 to 90 percent trichloroacetic acid (TCA) although TCA can also be used for vaginal or anal lesions. A small amount should be applied and allowed to dry until a white frosting develops. The patient should be instructed to wash the area with liquid soap or sodium bicarbonate if excess TCA is applied to non affected tissue [50].

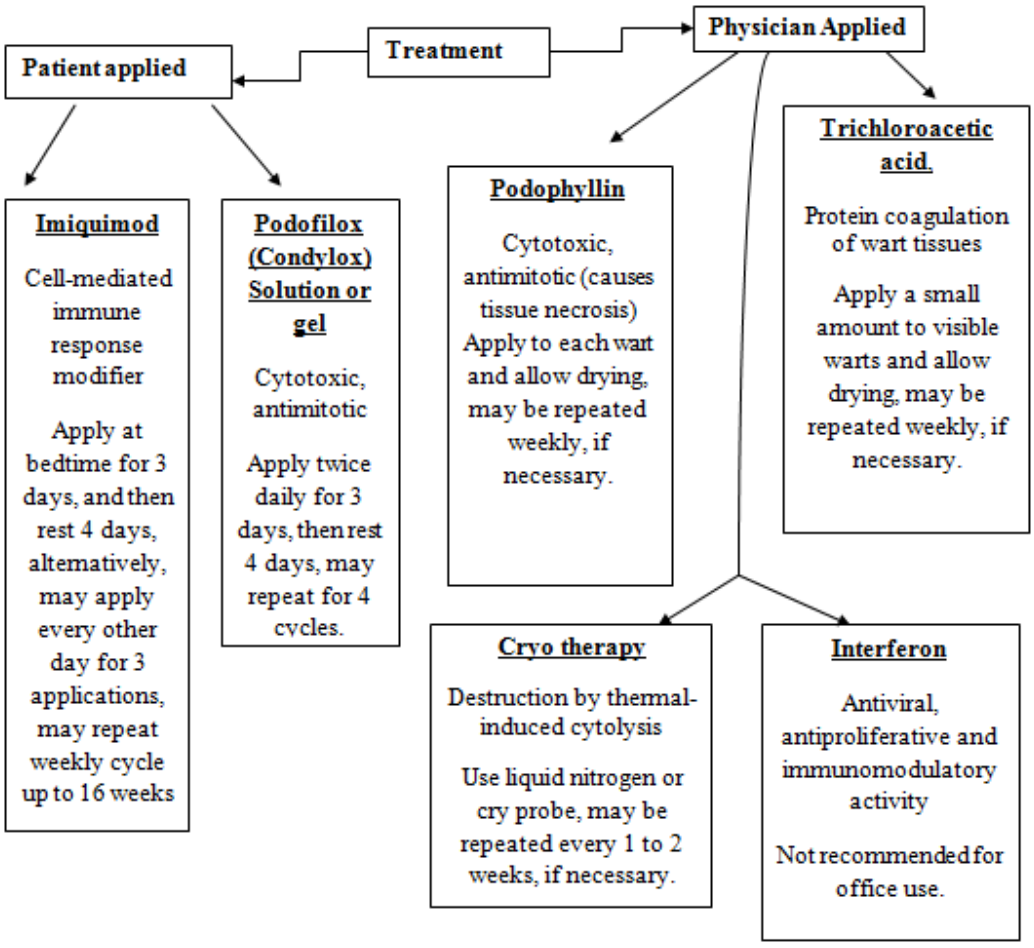

Figure 3, Mechanism of action and treatment cycles of selected treatment for patient with genital warts [30]

Table 1, Comparison of treatment for genital warts with adverse effects, response rate and recurrence rate [43-47]

Treatment	Wart	Adverse Effects	Response rate (%)	Reoccurrence rate (%)
Imiquimod (Aldara)	Genital warts	Erythema. flaking, edema, Irritation, ulceration, pain, minimal systemic absorption	30-50	15
Podophyllotoxin (Condylox),	Warts on moist surface	Pain, Inflammation, burning at application site, low risk for systemic toxicity	45-80	5-30
Cryotherapy with liquid nitrogen.	All warts	Painful and may result in blister or ulcer formation.	60-90	20-40
Interferon	Simple warts	Burning, itching, irritation at injection site, headache, fever	20-60	Insufficient data
Podophyllin	Warts on moist surfaces	Local irritation, ulceration, scarring. Systemic side effects may include fever, nausea, vomiting, confusion, coma,, renal failure,. Podophyllin is considered a teratogen and should not be used during pregnancy	30-80	20-65
Trichloroacetic acid.	Genital warts	Pain and ulceration, no systemic side effects	50-85	35
Electrosurgery	Condyl-oma	Scarring, pain, bleeding, risk for burning & allergic reaction	35-70.	**20**
CO_2 laser treatment	Genital warts	Same as electrosurgery, risk of spreading HPV via smoke plumes	25-50	5-50

Other Treatments [51, 52]

5 percent fluorouracil cream (Efudex)- It is no longer recommended due to teratogenicity and severe local side effects.

Intralesional injection of interferon- It is used only by subspecialists and not recommended for routine office use because of the high incidence of local and systemic side effects.

ABLATIVE TREATMENT

Cryotherapy

Cryotherapy is applied with a cryoprobe, liquid nitrogen spray, or a cotton-tipped applicator and recommended for patients with small to moderate numbers of warts. The cold source is applied and held until a halo appears around the circumference of the lesion (about 10 to 20 seconds). Local anesthesia (topical or injection) may be given to facilitate therapy if the area is large with number of warts. Trials have found similar response rates for cryotherapy as compared with podophyllin, TCA and electrosurgery [50].

Surgical treatment

Surgical treatment for warts involves removal to the dermal-epidermal junction. Options inc1)lude tangential scissor excision, shave excision, curettage, and loop electrosurgical excision procedure (LEEP). Treatment requires operator experience especially with LEEP, to avoid too deep a removal. The treatment requires local anesthesia although patient can be wart-free in one visit. This method is best if a large area is involved with many warts [53].

Laser Treatment

Carbon dioxide laser treatment is best for extensive intraurethral warts and extensive vaginal warts. Physicians performing this procedure should wear masks as laser treatment can create smoke plumes which contain HPV. Laser treatment may be useful in HIV-infected patients who have very large external genital warts or severe local symptoms [54].

ADVERSE EFFECTS OF TREATMENT

The side effects and risk of recurrence of each treatment method are summarized in Table 1. All the methods of treatment can cause considerable discomfort, erythema, epithelial erosion, ulceration at the treatment site, depigmentation and scarring. Treatment should be confined to affected skin to minimize the risk of side effects. There is little information available regarding the management of complications of therapy for genital warts, the use of non-prescription analgesics is an option to relieve discomfort [30].

Patient counseling and education helps to prepare the patients for possible adverse effects and outcome of therapy. Patients must understand that HPV infections cannot be cured but treated. They must understand that affected men

and women, and sex partners of affected patients, are at risk for cervical or genital cancer, and affected women and female sex partners of affected men should have regular Pap smears performed.

SELECTION OF TREATMENT OR MANAGEMENT OF GENITAL WART [38]

The choice of treatment is considered by a number of factors, including wart location, morphology, size and number. Many treatment recommendations are based on expert opinion and experience. Very few studies have compared different treatments. Patients should be told that no treatment ("watchful waiting") is an option for warts at any site, especially for warts in the vaginal and anal canal [43]. Figure 4 summarizes a suggested approach to treatment selection [43].

COST ANALYSIS

A cost-effectiveness analysis has found that treatment for simple genital warts with podophyllin resin, TCA, and imiquimod were more expensive than interferon treatment. Podofilox remains the least expensive patient-applied treatment for extensive condyloma that requires prolonged treatment, Surgical excision, LEEP, and electrodesiccation were inexpensive as compared to cryotherapy and spodophyllin resin. Interferon remained the most expensive alternative treatment [45, 50].

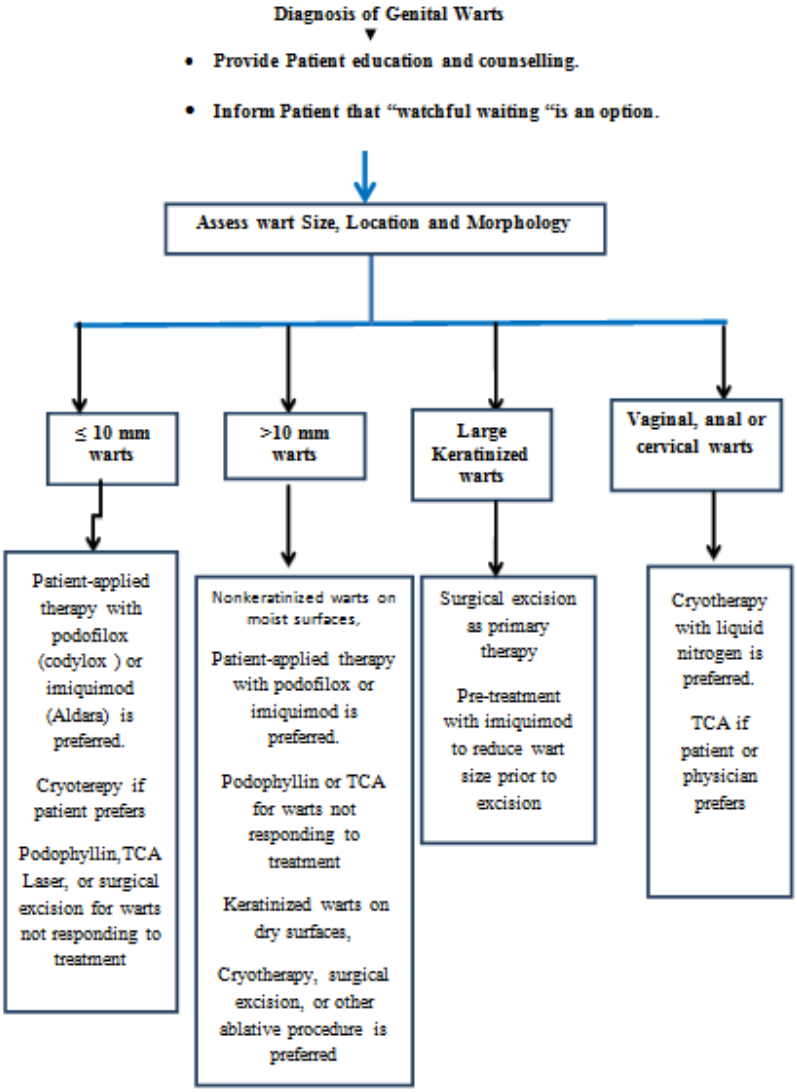

Figure 4 Selection of treatment in patients with genital warts. (TCA - trichloroacetic acid)

SPECIAL TREATMENT ISSUES

Subclinical Warts

Colposcopy, biopsy, acetic acid application, laboratory identification of HPV serology are some of the methods used to identify ubclinical genital HPV infection (i.e., anogenital HPV infection without evident exophytic warts). Early treatment of subclinical warts has not shown to favorably affect the course of HPV infection in patients or their sex partners with regard to reduction in HPV transmission, symptoms, and recurrence rates. Therefore, general patient population or patients with history of genital warts are not recommended colposcopy, acetowhite staining, or other methods to screen subclinical warts [1, 51]. Patients who have a history of warts should be counseled about the importance of cervical cancer screening as they are presumed to have latent HPV infection.

Large Warts

Surgical excision may be used as primary therapy for warts greater than 10 mm in diameter. To improve surgical outcomes, imiquimod cream may be applied for three to four treatment cycles to reduce wart size. Imiquimod should be continued if patients have more than 50 percent reduction in wart size after three to four treatment cycles and further continued until warts clear or eight treatment cycles have been completed. Surgical excision or other ablative therapy should be initiated, if patients have a less than 50 percent reduction in wart size after the initial treatment cycles [30].

Pregnancy

The main goal of treatment in pregnant women is to minimize neonatal exposure to the virus by reducing the number of lesions present during delivery. Infected children may have complications of anogenital warts and laryngeal papillomatosis. Podophyllin, podofilox, and fluorouracil should not be used in pregnant patients because of possible teratogenicity. Imiquimod can be considered for use in pregnant women after informed consent has been obtained [51]. TCA has been used in pregnant patients without adverse effects. Surgical excision, cryotherapy, and electrocautery are appropriate treatment options during pregnancy if treatment is required. Cryotherapy is safe if only three to four treatments are given, based on the study of 34 pregnant women demonstrating the safety of cryotherapy treatments [56].

Immunocompromised Patients

Poor response, increased relapse rates and higher risk of dysplasia is observed in patients with suppressed cell immunity associated with organ tsransplantation, HIV infection or other conditions [30].

WAYS TO PREVENT HUMAN PAPILLOMAVIRUS (HPV) FROM SPREADING [23, 57]

One can do several things to lower the chances of getting HPV.

Get vaccinated.

HPV vaccines are safe and effective.

They can protect both male and female against diseases (including cancer) caused by HPV when given in the recommended age groups

HPV vaccines are given in three shots over six months, it is important to get all the three doses.

Get screened for cervical cancer.

Routine screening for women aged 21 to 65 years old can prevent cervical cancer.

If sexually active

Refrain from sexual activity until treatment is complete.

Check the sexual partners

Have sex only with someone who only has sex with you i.e. be in a mutually monogamous relationship.

Use latex condoms in the right way. This can lower the chances of getting HPV. They offer some but not complete protection as HPV can infect areas that are not covered by a condom.

General cautions

Eat healthy diet, quit smoking. Smoking affects the body's ability to fight infection and women who smoke often take longer to clear the wart viruses. Smoking is also a risk factor for the development of cervical cancer.

Daily exercise helps the body's immune system which in turn will fight the human papillomavirus (HPV).

Do not try any home remedies or over-the-counter drugs to remove warts on the genital or anogenital area because the skin can be damaged as the genital or anal area is too sensitive for these products.

HPV VACCINES

HPV infection is considered to contribute almost 100% cervical cancers and at least 80% of anal and 40–60% of vulvar, vaginal, and penile cancers. At present, two prophylactic HPV vaccines licensed globally are available in India and both are prepared from purified L1 structural proteins. These proteins self-assemble to form virus-like particles that induce a protective immunity. Gardasil™ (marketed by Merck) is a quadrivalent vaccine against HPV types 6, 11, 16, and 18 and recommended for use in females 9–26 years of age, for the prevention of cervical, vulvar, and vaginal cancers and intraepithelial neoplasia and condylomaacuminata and recently for vaccination in boys and men 9–26 years of age for the prevention of genital warts. Cervarix™ (marketed by Glaxo Smith Kline) is a bivalent vaccine approved for the prevention of cervical cancer and precancerous lesions caused by HPV 16 and 18, in females 10–25 years. Both HPV vaccines are safe and efficacious against type-specific HPV-induced anogenital warts, precancerous lesions, and cervical cancer. The vaccines are most effective when given before the onset of sexual activity and provide long-term protection [10, 18].

CONCLUSION

Genital warts are benign manifestations of human papillomavirus (HPV) types 6 and 11 that can cause discomfort and significant patient distress. They are clinically present in 1% of sexually active U.S. population with an estimated lifetime risk of about 10%. Prevalence varies with age,the highest is in sexually active women 20 to 24 years of age and in men 25 to 29 years of age. Warts vary from small, flat-topped papules to large cauliflower like lesions on the anogenital mucosa. Treatments may be applied by the patient or by a clinician. Patient- applied treatments include imiquimod, podofilox and clinician- applied treatments include podophyllin, trichloroacetic acid. Surgical treatments include excision, cryotherapy and electrosurgery. Male circumcision may also be effective in decreasing the transmission of human papillomavirus. Two vaccines are available against the virus that cause genital warts in men and women. Effective vaccination coverage in young adolescent males and females will substantially reduce the incidence of these anogenital malignancy-related morbidity and mortality. Thesre is need to generate India-specific data on HPV epidemiology and HPV vaccination efficacy as well as continue worldwide surveillance and development of newer vaccines. Vaccination alone will not be successful unless it is coupled with education about healthy sexual behavior and information about the diagnosis and treatment of precancerous lesions and cancer.

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