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Gynaecological Implications of HPV Infection & Strategies to Prevent HPV Infection

P. Reddi Rani[1], K. Sathyanarayana Reddy[2]

[1]Professor of Obstetrics & Gynaecology, Mahatma Gandhi Medical College & Research Institute, Pondicherry 607402, India

[2]Professor of Radiation Oncology, Mahatma Gandhi Medical College & Research Institute, Pondicherry 607402, India

Abstract: ***HPV infection is one of the most common sexually transmitted disease. Prevalence of HPV infection in general population globally is high around 13.3%, in India it is estimated to be 7.9%. While majority of HPV infections are self-limiting and regress spontaneously, they still account for about 70% of anogenital cancers globally. Types 16 and 18 are most common oncogenic subtypes. Mode of infection, clinical manifestations and pathogenesis of malignancy are discussed. Management of non-malignant, pre malignant lesions is also discussed. While HPV infection and its prevention cannot be completely eliminated it can be reduced by using preventive measures like counseling, safe sex practices, barrier contraception and most importantly using HPV vaccinations. Cervical cancer screening will help in diagnosing premalignant lesions and early malignancies. Bi-valent, quadri-valent and more recently the nine valent vaccines are available which are safe and effective in preventing HPV infection.***

Keywords: HPV, Venereal warts, Premalignant lesions, Cervical cancer, HPV vaccines

1. Introduction

Human Papilloma Virus (HPV) is a small double stranded DNA virus that infects the epithelium and is one of the most common sexually transmitted disease. More than 120 HPV subtypes have been identified and currently around 40 subtypes are known to infect the anogenital tract of humans causing diseases ranging from benign genital warts to invasive carcinoma of genital tract. Most HPV infections are self-limited and are asymptomatic or unrecognized. Most sexually active persons become infected with HPV infection at least once in their life time. Persistent oncogenic HPV infection is the strongest risk factor for the development precancerous and cancerous lesions of the anogenital tract[1].

2. Epidemiology

The overall prevalence of HPV of any type was 13.3% and the prevalence of oncogenic types was 9.6%. Highest rates of incidence for oncogenic types were in 20-24 years age group and lowest in 40-44 years age group. Rates increase again in 45-49 years age group. Incidence rates in adolescents (15-19yrs) is 15.7%[2].

Prevalence of HPV in the general population of India is about 7.9%. Cancer incidence is generally expressed as age adjusted or age standardized rate (AAR). AAR for Indian women for cervical cancer is 27/100,000. Types 16 and 18 account for 70% of cases of cervical cancer globally. A meta-analysis of HPV type distribution from India showed HPV type 16 was the predominant (64.8%) in invasive cervical cancer followed by HPV 18, 45, 33, 35, 58, 59, 31[3].

3. Pathogenesis

HPV infection usually occurs in skin and sometimes in mucosa. The HPV replication cycle begins with entry of the virus into the cells of the basal layer of the epithelium which may require mild abrasion or micro trauma of the epidermis. Once outside the host cell HPV DNA replicates and progresses to the surface of the epithelium. Infection with specific sub types is necessary for the development of cervical cancer and their immediate precursor lesions.

The four major steps in the development of cervical cancer[4] are: (Fig. 1)

1) Infection of the metaplastic epithelium of transformation zone with one or more carcinogenic HPV types.
2) Viral persistence rather than clearance reflecting host immune response.
3) Clonal progression of persistently infected epithelium to cervical cancer precursors.
4) Invasion.

Persistent infection and integration of viral DNA into host cell genome is essential for carcinogenesis.

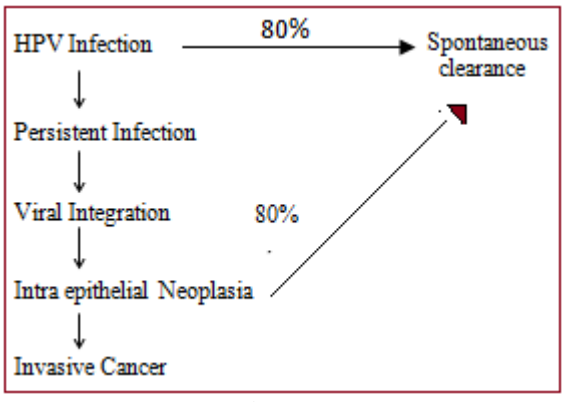

Figure 1

The E-6 and E-7 are the primary HPV oncoproteins with numerous cellular targets. The activity of these viral oncoproteins results in genomic instability leading to malignant phenotype. E-6 protein of high risk HPV types bind the tumor suppressor protein P-53 and causes degradation of P-53, removes the P-53 dependent control of the host cell cycle and leads to development of precancerous lesions and cancer of the cervix[5].

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The E-7 gene product is a nuclear phosphoprotein that associates with the product retinoblastoma gene (PRb) which is a tumor suppressor gene protein in the negative control of cell growth. E-7 is the primary transforming protein. Deregulation of P-53 by E-6 and the functional inactivation of PRb by E-7 expression is the mechanism of HPV related cancers[6]. In addition to the effects of activated oncogenes and chromosome instability, potential mechanism contributing to the transformation include methylation of viral and cellular DNA telomerase activation, hormonal and immunogenetic factors.

Virus infects the keratinocytes in the basal layer of stratified epithelium or the mucosal cell lining of critical sexual areas such as mouth, anus and vagina. HPV infection in these cells leads to the activation of a cascade of viral gene expression and production of HPV virions.

HPV does not always cause clinically visible lesions.

1) They can be exfoliated with the superficial keratinocytes leaving behind no trace of previous infection.
2) They can remain silent with in the cell DNA.
3) They can be active in DNA producing benign proliferation or promote positive transformation of a normal cell into a cancerous one. Fortunately most infections clear. Persistent infection with high risk type will lead to high grade intraepithelial neoplasia and cancer.

Mode of Transmission

Though transmission through vaginal, oral and anal sex are common it can also occur with skin to skin contact. Rarely transmission can occur in fetus through vertical transmission if mother has warts in the vagina and has vaginal delivery. Child can develop warts in the throat giving rise to recurrent respiratory papillomatosis.

Risk Factors

Risk factors for HPV include:
Early age at sexual activity
Higher number of sexual partners
Co-infection with other sexually transmitted diseases like *Herpes simplex* and *Chlamydia trachomatis*
Immune compromised status especially HIV and AIDS
Non-consistently protected sex
Smoking

Types of HPV Infection & Lesions Caused by them

1) Low risk or non-oncogenic such as types 6 and11 cause benign or low grade cervical cell abnormalities, genital warts and laryngeal papillomas. They can cause genital warts on cervix, vagina, vulva and anus in women.
2) High risk or oncogenic HPV types 16,18,31,33,35,39,45,51,52,56,58,59,68,69,73,82 can cause low grade cervical abnormalities, high grade cervical cell abnormalities that ae precursors to cancer and anal cancer. In addition to these cancers they are also associated with cancers of vulva and vagina.

Most HPV infections of the cervix are asymptomatic and more than 90% of detected infections are cleared within 2 years. High risk HPV types are detected in 99% of cervical cancers. Type 16 is the cause of approximately 50% of cervical cancers worldwide and types 16 & 18 together account for about 70% of cervical cancers[7].

Lesions caused by low risk HPV types:

Visible manifestations of HPV are seen only in minority of cases. Average latency period is 3-4 months and clinical lesions may appear 3 weeks to years after initial exposure.

1) Genital warts: They are usually multiple, asymmetric and polymorphic; present as exophytic papules typically seen on moist non hair bearing skin involving the vulva, vagina, cervix, perineum and anal region. They can become confluent or progress to large pedunculated cauliflower like masses. Sessile plaque like lesions may be seen in the vagina. Left untreated they may regress spontaneously or persist and grow. There is usually no need to do biopsy to exclude malignancy unless they are atypical, pigmented and not responding to treatment. They have to be differentiated from condylomata lata, molluscum contagiosum, seborrheic keratosis etc.
2) Abnormal PAP smears: HPV associated intraepithelial neoplasia most commonly involve uterine cervix but may also be found in vulva, vagina and anus. They are associated with 0-25% of abnormal cervical smears like ASCUS and LSIL and rarely with HSIL, AGC/AGCUS and cancer. Most infections are transient and clear within 6 months to 2 years. Long term persistent infection with certain HPV subtypes especially at high viral load is a strong risk factor of HSIL and cancer[8].

Diseases caused by high risk HPV:

1) Flat warts also known as Bowenoid papulosis or warty VIN are usually caused by high risk HPV seen on skin of genitalia as slightly raised popular or macular lesions with or without keratinization and brown, grey or blue pigmentation.
2) Cervical cancer and its precursors: Normally most infections resolve spontaneously within 2-3 years. As the viral infection persists, it integrates into the human DNA and can lead to cancer precursors likemoderate to severe CIN or carcinoma in-situ and if not treated lead to invasive cancer[9].
3) Vaginal intraepithelial neoplasia (VAIN) and vaginal cancer
4) Vulvar intraepithelial neoplasia (VIN) and vulvar cancer
5) Anal intraepithelial neoplasia (AIN) and anal cancer

Genital lesions associated with HPV infection[10]

Condition	*HPV Subtypes*
Condyloma acuminatum	6, 11
Verrucous carcinoma	6, 11
Bowenoid papulosis	16,31,32,34,35,37,42
Intraepithelial neoplasia Invasive carcinoma (cervix, vagina, vulva, anus)	16,18,31,33,35,39,42 43,44,45,51,52,56

HPV related lesions in HIV infected patients:

The prevalence of HPV in HIV infected patients is higher than non HIV infected individuals and varies with degree of immune suppression[11].

1) Condyloma acuminatum, anal intraepithelial neoplasia (AIN), CIN have been reported to occur more frequently.
2) Increased severity of HPV disease

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3) HPV is more difficult to treat and more likely to recur with increased immunosuppression
4) Patients with AIDS have an increased risk of developing in-situ or invasive genital cancer.

4. Diagnosis

It is by clinical examination and lab tests

PAP smear: the cervical PAP smear is one of the most effective indicator of HPV infection. Cytological changes such as koilocytosis, nuclear atypia, delayed maturation, hyperkeratosis and parakeratosis are all associated with HPV infection. Cytological examination of cervical smears can detect abnormalgrowth of squamous cells in the form of squamous intraepithelial lesions low or high grade depending on how much cervical epithelium is affected. Similar changes are seen in vagina and vulva. It can cause adeno carcinoma in-situ also. All these changes can be detected by PAP smear using either conventional or (LBC) liquid based cytology. LBC is preferred as it reduces false negative rates and same solution can be used for HPV DNA testing. Abnormalities associated with high risk HPV types are ASC-US, ASC-H, LSIL, HSIL, atypical glandular cells and cancer cells. These abnormalities should be referred for colposcopy. PAP smear is cost effective, useful for widespread use. It diagnoses precancerous lesions with false positive rates of less than 1% but has limitation of repeated tests to be performed, low sensitivity and specificity and flies negative rate of 15-40%[12].

Anal cytology should be done in women with abnormal cervical, vaginal or vulvar histology to decrease the incidence of invasive anal cancer and to detect dysplastic lesions in high risk women using a Dacron swab which is a well validated technique comparable to cervical cytology[13].

Colposcopy
Women with abnormal smear or cases where symptoms and signs are suggestive of cancer should be referred for colposcopy andif necessary colposcopy directed biopsy.Endocervical curettage is done in glandular lesions or when transformation zone is not visualized in its entirety.

HPV DNA Testing: Indications[14]
1) In women with ASCUS to determine the type of follow up either with colposcopy or with PAP smear in 1 year.
2) As an adjuvant to cervical cytology in women ≥ 30years to reduce false positive rate of conventional cytology and increase the negative predictive value.

In women younger than 30 years there is no need for HPV testing as detection of HPV infection in a woman under age 30 years is likely to represent incidental infection which may clear spontaneously. Women with LSIL, HSILand SCC are usually associated with high risk type who will require direct colposcopy and biopsy rather than HPV DNA testing.

Hybrid capture 2 test has high sensitivity and detects five low risk and thirteen high risk HPV types and do not use radioactivity. PCR test to detect HPV DNA is highly sensitive.HPV DNA for non-oncogenic types is not recommended[15]. HPV testing including for oncogenic types should not be performed in the following situations:
1) For making a decision to vaccinate or not against HPV
2) For conducting STD screening
3) Conducting screening for carcinoma cervix as a stand-alone test
4) Testing women aged < 30 years as a part of routine cervical cancer screening
5) Testing oral or anal specimen

Anoscopy should be done in women with anal PAP test and biopsy in women with HSIL and HIV positive. Urethroscopy to be done in women with extensive urethral warts.

5. Special Situations

Pregnancy
Pregnant women are screened at same intervals as nonpregnant women. Abnormal test results are referred for further investigations. Drugs like podophyllin and imiquimod are contraindicated in pregnancy. Vaccination should not be recommended and postponed. Cesarean delivery is indicated for women with anogenital warts causing obstruction or if vaginal delivery might result in excessive bleeding. Rarely HPV types 6& 11 can cause respiratory papillomatosis in infants and although routes of transmission whether transplacental, perinatal or post-natal is not completely understood.

HIV
They are at increased risk of cervical cancer and precancerous lesions. They should be screened within one year of sexual activity or at initial HIV diagnosis using either conventional or liquid based PAP test. It should be repeated six months later[16].

Adolescents
Prevalence of oncogenic HPV types are high among adolescents aged<21 years and squamous intraepithelial lesions caused by HPV in adolescent girls are more likely to regress than in older women. Hence screening with PAP smear and HPV DNA is not recommended. But in HIV infected women they should be screened within one year of sexual activity because of higher rates of progression of abnormal cytology[17].

Treatment of External Genital Warts
Aim of treatment is removal of warts and amelioration of symptoms if present. Big warty lesions also cause significant psychosocial distress and removal can relieve cosmetic concerns. They can regress spontaneously, remain or progress.

Recommended Regimens
Treatment depend on wart size, number, anatomic site, cost, convenience and adverse effects. No evidence exists as to which one treatment is better than the other, may require combination therapy.

Self-Applied Treatment:
1) Podophyllotoxin: It is applied as 0.5% solution to warts every 12 hours, 3 days a week for up to 6 weeks. With

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this treatment 45-88% of warts clear but recurrence rate is as high as 60%[18]. It is teratogenic and is contraindicated in pregnancy. It acts as an antimitotic agent interfering with cell division and damaging tissues in which cells are reproducing.

2) Imiquimod: It is applied as 5% cream applied 3 times a week topically to the lesions up to16 weeks. 72% of EGW were cleared and 50% reduction in size in 81% of persistent warts. Recurrence rate was only 13%[19]it is a cellular immunomodulator and acts by inducing costly.

Provider-Applied Topical Treatment:

1) Podophyllin resin 10-25%-removes warts by destroyinginfected tissues with a locally destructive and anti-proliferative action. It is not used routinely because of side effects and due to availability of better drugs.
2) Trichloroacetic acid- it is applied directly over the wart protecting the surrounding skin with petroleum gel. It is cheap, safe in pregnancy, easy to use and minimal systemic reaction. Occasionally it causes skin blisters and ulceration. Treatment can be repeated weekly for 4-6 weeks
3) Interferon α and β- these are administered intra lesionally and systemically for recurrent or resistant lesions. It is expensive and is associated with systemic toxicity.

Provider-Applied Ablative Treatment:

Ablative/excision treatments are advised when medical therapy fails.

1) Cryotherapy using liquid nitrogen- it destroys warts by thermal introduced cytolysis, safe in pregnancy and has no systemic side effects. May cause pain and ulceration.
2) Laser vaporization- it is efficacious, precise and has no systemic reactions. It is useful when other modalities of treatment failed. In patients with large extensive warts or for intraurethral warts it can be used. Healing time is long, needs a trained person and is expensive.

Excision:

1) LEEP- Large loop excision of transformation zone especially if they are associated with intra epithelial neoplasia.
2) Surgical excision- For large exophytic condylomata or confluent vulvar intra epithelial neoplasia. Surgical therapy has the advantage of eliminating warts at a single visit although recurrences can occur.

Management of warts in urethral meatus, vagina, cervix and intra anal warts is excision either with cryotherapy using liquid nitrogen or surgical removal. In vaginal, cervical and anal warts,trichloroaceticacid (80-90%) can be used. In exophytic warts HSIL should be excluded[15].

In case of EGW, it is usually expectant management and if treatment is required it is by application of trichloroacetic acid or cryotherapy.

In immune suppressed women especially in HIV infected patients more than one method of treatment and longer duration of therapy is often needed.

Treatment of all dysplastic lesions of cervix, vagina and vulva will be done as per protocols like cryotherapy, LEEP, laser ablation or conization and regular follow up. Treatment of invasive cancers will be as per protocols.

Follow up:

Majority of anogenital warts respond within 3 months, unless the woman is immunocompromised and or treatment has been improper. Complications occur rarely. They may be hypo/hyper pigmentation and chronic pain syndrome.

Management of sex partners:

Counselling of partners is important as he might have HPV infection without visible signs. HPV DNA testing is not needed, but should have a physical examination and tests for detecting other STDs. Barrier contraception should be advised.

6. Prevention

HPV transmission can be reduced but cannot be eliminated. Various preventive measures are

1) Counselling:HPV infections and their complications result in a wide range of emotional responses and depression. Reassurance is needed, HPV infections are very common and most are asymptomatic. Persistent infection needs to be followed up by PAP smear to detect early/ pre invasive lesions. Treatment of these lesions will prevent invasive lesions. Cervical cancer is a rare complication and can be prevented with close monitoring.
2) Safe sex practices: Avoid multiple sexual partners, monogamy decreases the incidence.
3) Barrier contraception: Use of condoms consistently reduces HPV infection. However infection can still occur due to skin to skin contact in areas not covered by condom.
4) Cervical cancer screening should continue based on guidelines.
5) HPV vaccine: the HPV L-1 protein, the antigen in the vaccine is produced with the use of recombinant techniques. The protein assembles itself into virus like particles (VLP) that are identical to HPV virions morphologically but without the viral DNA core.

VLP vaccines induce a virus neutralizing antibody response but pose no infectious or oncogenic risk[20]. With these facts in consideration 3 HPV vaccines have been developed, which are highly immunogenic and are very effective in preventing persistent HPV infection in women not previously infected with HPV types used in the vaccine. Antibody response develops within one month after completing the 3 dose series.

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Characteristics of HPV vaccines

Characteristic	Bivalent (2V-HPV)	Quadrivalent (4V-HPV)	Nine valent (9V-HPV)
Brand name	Cervarix	Gardacil	Gardacil-9
Manufacturer	Glaxo-Smith Kline	Merck & Co	Merck & Co
VLPS	16, 18	6,11,16,18	6,11,16,18,31,33,45,52,58
Volume per dose	0.5 ml	0.5 ml	0.5 ml
Mode of admin.	IM	IM	IM
Number of doses & interval (months)	0, 2, 6	0, 2, 6	0, 2, 6

Second dose two months after first dose, third dose 6 months after first dose.

7. Current Recommendations

The advisory committee on the immunization practices[21] recommends routine HPV vaccination at age 11 or 12 yrs. The vaccination series can be started beginning at age 9 yrs. Vaccination is also recommended for females aged 13 through 26 years and for males 13 through 21 years who have not been vaccinated previously or who have not completed 3 dose series. The 9- valent HPV vaccine was approved by FDA on 10thDec 2014. The vaccine targets HPV types 6, 11,16,18,31,33,45,52, and 58. The antibody response generated for HPV types 6, 11, 16 and 18 is not inferior to quadrivalent vaccine[22].

Contraindications:

1) Allergic reaction to any component of HPV vaccine or to a previous dose of vaccine.
2) Pregnant women. If a woman is found pregnant after initiating the vaccination schedule, the remaining doses should be delayed until completion of pregnancy. Even if vaccine is administered no intervention is needed. Cervical cancer screening recommendations will continue as usual even in vaccinated women[23].

7.1 Adverse Effects

No serious adverse reactions reported. Swelling, red ness, pain and sore ness at the site of injection have been reported. Vaccines are highly immunogenic and have a seroconversion rate of> 99.75% within one month after completing the 3rd dose and the protection is maintained for more than 6 years. HPV study group[24]reported that the duration of protection is up to 6.4 years after first vaccinationalong with high and sustained immunogenicity and favorable safety of HPV 16/18 AS04-adjusted vaccine. Further studies are needed to evaluate the need for revaccination or booster doses.

7.2 Cost Effectiveness

A program of vaccination that permits a later age of screening and less frequent screening intervals is likely to be cost effective. The HPV type 16 & 18 will reduce the life time risk of developing cervical cancer by 46-66%[25]. Government agencies should advocate for public funding to evaluate cost benefit analysis. It should be included in routine immunization program. Awareness and knowledge of vaccine should be disseminated amongst parents.

Vaccination can be administered to women younger than 27 years with a previously abnormal PAP test /HPV DNA test positive, but it does not have any therapeutic effect on existing HPV infection or cervical lesion. HPV DNA test is not a prerequisite for vaccination. Vaccine can also be administered to immune suppressed women and women who are breast feeding.

8. Conclusion

HPV infection is one of the common sexually transmitted diseases associated with a spectrum of diseases ranging from benign warts to invasive carcinoma of the anogenital tract. Most infections are asymptomatic and clear spontaneously. Only the persistent infection will lead to carcinogenesis. Prevention to a large extent is possible by safe sex practices, counselling, health education and HPV vaccination.

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