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Brief Report

Human papilloma virus vaccination: practical guidelines

Kiran Yadav[1]*, Kaushal Yadav[2], Sabhyata Gupta[1]

[1]Department of Gynaecology and Gynaec-oncology, Medanta, Gurgaon, Haryana, India
[2]Department of Surgical Oncology, Tata Memorial Hospital, Mumbai, Maharashtra, India

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***Correspondence:**
Dr. Kiran Yadav,
E-mail: kiranyadav05@yahoo.in

ABSTRACT

Cervical cancer has a long latency period and established role of HPV lead to interest in development of HPV vaccine. Main goal of HPV vaccination is to decrease cervical cancer incidence. There are two vaccines available, for the prevention of HPV infection - gardasil and cervarix. Gardasil is quadrivalent and cervarix is bivalent. The FDA has approved gardasil in 2006 and cervarix in 2009 based on their efficacy in phase 3 trails. When recommending HPV immunization of females, it should be offered to girls 11 to 12 years of age, but can be administered as early as nine years. Catch-up vaccination should be offered for females aged 13 to 26 years who have not been previously vaccinated. HPV immunization is not effective in clearing cytological evident disease or HPV infection that is already present and it does not provide immunization for serotypes other than included in vaccine. Cervical cancer screening is recommended to continue as per guidelines.

Keywords: HPV vaccination, Carcinoma cervix, Cancer vaccination

INTRODUCTION

Human papillomavirus is an epitheliotropic agent and there are more than 100 genotypes.[1] Sexually transmitted genotypes are the documented cause of genital cancers and genital warts in females. Among female genital malignancies human papillomavirus (HPV) is detected in 99.7 percent of cervical cancers,[2] 60-65% of vaginal cancer[3] and 30-50% of invasive vulval cancer.[4] High risk HPV types are attributed for cervical cancer while low risk types are detected in anogenital infections but not in cancer. HPV types 16 and 18 cause approximately 70 percent of cervical cancers and 50 percent of precancerous cervical lesions. HPV 16 and HPV 18 cause approximately 60 percent of HPV-positive vaginal cancers and precancerous vaginal lesions, HPV 16 and HPV 18 cause approximately 35 percent of HPV-positive vulvar cancers and 75 percent of precancerous vulvar lesions.[5] HPV types 6 and 11 also cause 90 percent of genital warts. Genital warts are associated with physical and psychological morbidity and have a high rate of treatment failure.[6]

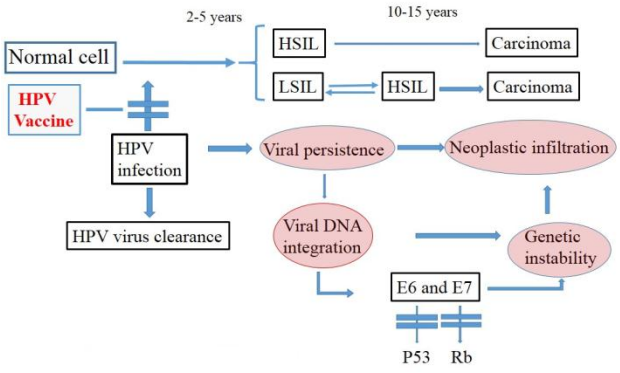

Figure 1: Cervical cancer and HPV vaccine.

Cervical cancer is a preventable disease and Pap smear screening has resulted in its decreased incidence rate.

Cervical cancer has a long latency period and established role of HPV lead to interest in development of HPV vaccine. Main goal of HPV vaccination is to decrease cervical cancer incidence, although it also reduce incidence of other HPV associated cancers. Principle basis of HPV vaccination is that high level expression of L1 major structural viral proteins lead to self-assembly in Virus Like Particles (VLP) which act as immunogens.

AVAILABLE VACCINES

There are two vaccines available, for the prevention of HPV infection - gardasil and cervarix. Gardasil is quadrivalent and cervarix is bivalent. The FDA has approved gardasil in 2006 and cervarix in 2009 based on their efficacy in phase 3 trails.

Gardasil is a quadrivalent HPV vaccine, against HPV types 6, 11, 16, and 18 [7]. It is composed of 20 micrograms each of HPV types 6 and 18 L1 capsid protein-based Virus-Like Particles (VLPs) and 40 micrograms each of HPV types 11 and 16 L1 capsid protein-based VLPs, with 225 micrograms amorphous aluminum hydroxyphosphate sulfate as an adjuvant. Two large randomized clinical trials in more than 17000 adolescents and young females proved its efficacy.[26,33] Among HPV-naïve populations, quadrivalent HPV vaccine prevents CIN2 or more severe disease in 97 to 100%. In overall population with or without prior HPV infection, efficacy was 44 percent at follow-up of three years. This may be because vast majority of enrolees in this trial were already sexually active and previously infected with vaccine HPV types. Munoz et al showed that quadrivalent vaccine prevents CIN2/CIN 3 in 100%.[8]

Cervarix is a bivalent vaccine which is against HPV types 16 and 18.[9] It is composed of 20 micrograms each of HPV types 16 and 18 VLPs with a novel adjuvant ASO_4, which contains 500 micrograms aluminium hydroxide and 50 microgram 3-O-desacyl-4' monophosphoryl lipid A (MPL), a detoxified derivative of the lipopolysaccharide (LPS) of the gram-negative bacterium Salmonella minnesota R595 strain. One large randomized clinical trial in more than 18000 young females aged 15 to 25 years proved its efficacy.[21]

Among HPV-naïve patients, the efficacy of the bivalent vaccine for preventing CIN2 or more severe disease was 93%, comparable with the efficacy of the HPV quadrivalent vaccine. In overall population with and without prior HPV infection, vaccine efficacy for preventing CIN2 or more severe disease was 53% at a mean follow-up of three years. These data are similar to those of HPV quadrivalent vaccine and emphasize the need to vaccinate individuals before the onset of sexual activity to gain the greatest benefit and maximize cost effectiveness.

IMMUNOGENICITY

Excellent antibody responses have been reported following immunization with both quadrivalent and bivalent vaccines.[10-12] Following vaccination with the quadrivalent vaccine, titers after 18 months in females aged 9 to 15 years were two- to threefold higher than in females aged 16 to 26 years for all targeted types.[13] Following vaccination with the bivalent vaccine, titre after seven months in females aged 10 to 14 years was noninferior to that observed in females aged 15 to 25 years, and in some studies, measured up to two-fold higher.[14-16] The bivalent vaccine is more immunogenic than quadrivalent vaccine.[17] Whether the induction of higher serum titers against HPV 16 and 18 has any impact on the degree and duration of protection is unknown and there is no defined minimum threshold titre for protection.

TIMING OF IMMUNIZATION

Clinical trial data of vaccine efficacy in females suggest that immunization with HPV vaccine is most effective among individuals who have not been infected with HPV (e.g., patients who are "HPV-naïve"). Thus, the optimal time for HPV immunization is prior to an individual's sexual debut. Neither vaccine treats or accelerates the clearance of pre-existing vaccine-type HPV infections or related disease.

Females who are sexually active should still be vaccinated consistent with age-specific recommendations. A history of an abnormal Papanicolaou test, genital warts, or HPV infection is not a contraindication to HPV immunization.[22] However, immunization is less beneficial for females who have already been infected with one of more of the HPV vaccine types.

American cancer society (ACS) guidelines

ACS recommend that HPV vaccination should be routinely offered to females aged 11 to 12 years; immunization may begin at nine years of age.[29] However, the ACS recommends catch-up vaccination for females aged 13 to 18 years who have not been previously vaccinated or completed their vaccine series. The ACS notes that there is insufficient evidence to recommend for or against vaccination of females aged 19 to 26 years.

World Health Organization (WHO): WHO advise that the primary target for HPV vaccine should be females between 9-13 years.

Pregnant females: Although neither of the HPV vaccine contains live virus, use in pregnancy is not recommended because of limited data on safety.[24] Lactating females can receive the immunization series since subunit vaccines do not affect the safety of infant breastfeeding.[25]

If a woman receives the HPV vaccine before she knows that she is pregnant she should be reassured that there is no evidence that this vaccine will harm the pregnancy. In the FUTURE II trial, pregnancy occurred in 1053 females in the vaccine group and 1106 in the placebo group; no obvious anomalies attributable to vaccine were observed.[20] Females who have started the series, but become pregnant before completion of all three shots, may resume the series when postpartum.

If there is history of genital warts, abnormal cytology, or positive HPV DNA test result, then also it is not evidence of prior infection with any or all of the vaccine HPV types, and so vaccination can still provide protection against infection with HPV vaccine types, not already acquired. Thus, the Advisory Committee on Immunization Practices (ACIP) recommends immunization for females (up to 26 years of age) with any such history.[24,25]

However, these patients should be advised that vaccination will have no therapeutic effect on pre-existing HPV infection or cervical intraepithelial neoplasia, and the potential benefit of HPV vaccination is not as great as if, they were vaccinated before they started having sexual activity.

The ACIP does not recommend serologic or HPV DNA testing prior to immunization.[25]

VACCINE DOSE AND ADMINISTRATION

Immunization schedule - Immunization schedules are slightly different for the quadrivalent and bivalent vaccines. The quadrivalent vaccine (Gardasil) is administered in three doses at time zero, and at two and six months of follow-up. The bivalent vaccine (Cervarix) is administered in three doses at time zero, and at one and six months of follow-up.

Missed doses/alternate schedules - Patients often do not follow up for their immunizations on schedule.[26] The Advisory Committee on Immunization Practices (ACIP) recommends that if the vaccination series is interrupted for any length of time, it can be resumed without restarting the series. The same formulation should be used to complete the series, if possible.

Because of the frequency of missed doses and the suboptimal adherence to a three dose vaccine schedule, there has been interest in whether fewer doses or greater time intervals between doses remain effective.

In one study, vaccine efficacy of the quadrivalent vaccine remained high in persons who did not adhere to the recommended immunization schedule, including those who got fewer than three doses, suggesting some flexibility in the spacing of doses, although more data on the timing and number of doses and their impact on efficacy are needed before alternate dosing schedules can be adopted.[27]

The quadrivalent vaccine (Gardasil) is administered in three doses at time zero, and at two and six months of follow-up. The bivalent vaccine (Cervarix) is administered in three doses at time zero, and at one and six months of follow-up.

Vaccine efficacy

Efficacy in the intention-to-treat population tended to be lower in older women, women with more partners, and women with abnormal Pap test results. The efficacy of quadrivalent HPV vaccine against high-grade cervical intra-epithelial neoplasia remains high through 42 months post vaccination

Cerical cancer cannot be used as end point, but surrogate end points of HPV infection and high grade dysplasia have been shown to link to progression of invasive cancer. Survival advantage with vaccination has not been proven till now.

Vaccine safety - Both vaccines use Virus-Like Particles (VLPs), which mimic the viral capsid. VLPs do not contain genetic material and are produced in biologic systems, which have well-established safety records.[28] Both vaccines appear to be safe in the context of clinical trials, although more is known about the safety profile of the quadrivalent vaccine than the bivalent vaccine

CERVICAL SCREENING AFTER VACCINATION

Cervical cancer screening with cervical cytology (i.e., Papanicolaou test) has reduced the incidence and mortality of cervical cancer by more than 70% over the past six decades.[29] Cervical cancer screening continues to be of great importance since HPV immunization will not prevent approximately 25 to 30% of cervical cancers in HPV-naïve females and does not protect females already infected with carcinogenic HPV types against the development of cancer.

CONCLUSION

Persistent viral infection with carcinogenic HPV types causes virtually all cancer of the cervix and most cases of vaginal and vulval cancer. The carcinogenic types of HPV 16 and 18, which are targeted by the current HPV vaccines, cause approximately 70% of all cervical cancers worldwide. HPV immunization is most effective among individuals who have not yet been infected with HPV (e.g., before sexual debut).

Multicenter, double-blind, placebo-controlled trials have demonstrated efficacy of both quadrivalent and bivalent HPV vaccines against incident and persistent cervical HPV infection due to vaccine types and the development of cervical intraepithelial neoplasia.

Quadrivalent HPV vaccine also has demonstrated high efficacy against vaccine type-associated vaginal and vulvar intraepithelial neoplasia in addition to genital warts associated with HPV 6 and HPV 11.

When recommending HPV immunization of females, it should be offered to girls 11 to 12 years of age, but can be administered as early as nine years. Catch-up vaccination should be offered for females aged 13 to 26 years who have not been previously vaccinated. Serologic testing or HPV DNA testing is not required prior to immunization.

Immunization of immunocompromised or immunosuppressed individuals with the HPV vaccine, including those with HIV infection, following the same guidelines as for immunocompetent patients. Catch-up vaccination among these patients is recommended up to age 26 years.

Cervical cancer screening is recommended for any woman 21 years of age or older. Clinicians should be aware that HPV immunization is not effective in clearing cytological evident disease or HPV infection that is already present and it does not provide immunization for serotypes other than included in vaccine.

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