

Human papillomavirus, vaccines, and protection from cervical cancer

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ABSTRACT

لقد قامت الأبحاث والبيانات المنشورة في وقتنا الحاضر بلفت الانتباه إلى وجود العلاقة الواضحة بين فيروس الورم الحليمي البشري وسرطان الرحم. وبالرغم من ظهور طرق التنظير التي من شأنها تجنب المريض الإصابة بهذا المرض إلا أن سرطان الرحم يعد ثاني أكثر أنواع السرطان انتشاراً بين النساء. تؤثر أتماط فيروس الورم الحليمي البشري 16 و 18 على سطح القناة المخاطية الشرجية، كما أنها تشكل ما نسبته 70% من حصيلة الإصابة بسرطان الرحم، و90% أو أكثر من حالات السرطان الشرجية. وعندما تأخذ العدد 493.000 من الحالات الجديدة المصابة بسرطان الرحم، والعدد 274.000 من الوفيات سنوياً يعين الاعتبار فإن سوف نعي مدى ضرورة طرق العلاج والوقاية من فيروس الورم الحليمي البشري. وباللجوء إلى الدراسات الوبائية الجزيئية التي تركز على تكون مثل هذا الورم والتركيب المناعي الحيوي للفيروس فإن الإستراتيجية الرئيسية تتمحور حول اللقاحات الوقائية والعلاجية. ونستعرض في هذا المقال البيانات المنشورة حديثاً حول فيروس الورم الحليمي البشري واللقاحات المستخدمة لهذا الفيروس.

Current published data makes clear the relationship between genital human papillomavirus (HPV) infection and cervical cancer. Although there is an opportunity for screening programs that could obviate the disease, cervical cancer still remains the second most common cancer among women worldwide. The subtypes HPV 16 and 18 affect the anogenital tract mucosal surfaces, and accounts for nearly 70% of all cervical cancers, and 90% or more of anal cancer cases. When the 493,000 new cases of cervical cancer and 274,000 deaths per year are taken into consideration, the importance of treatment and prophylaxis modalities for HPV can clearly be recognized. With the molecular and epidemiological studies that have focused on the oncogenicity and immunobiological structure of HPV, the main strategy is to develop prophylactic and therapeutic vaccines. Here, recent data concerning HPV infections and vaccination is discussed.

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Cervical cancer is a condition that threatens public health worldwide as the second most common cause of death in women with cancer, and is associated with the human papillomavirus (HPV).¹ The HPV prevalence at any given time in women with normal cytology approximates 11.7%, and this situation brings HPV to the top most levels among sexually transmitted infections. In a study of Turkish patients, HPV 16 testing positive in cervical intraepithelial neoplasia (CIN) 1 was found to be 12.5%, 19.4 % in CIN 2, 46.3% in CIN 3, and 83.3% in invasive cervical cancer specimens.² This virus family, which was thought to be associated only with unimportant warts on the skin and mucous surfaces until approximately 30 years ago, now has data showing that it is responsible for severe morbidity and mortality. For the development of cervical cancer, it appears that contagion with a persistent oncogenic HPV type is necessary, therefore in 99.7% of cervical cancer cases, HPV DNA was determined to be positive.³ The HPV 16 and 18 subtypes, which are true carcinogens and infect anogenital tract surfaces, lead to approximately 70% of cervical cancers, and 50% of precancerous cervical lesions, and also cause 72% of anal cancers, and 69% of precancerous anal lesions, and are particularly important.^{3,4} The same subtypes are also detected in 40-50% of vulvar, vaginal and penile cancers, and 10-12% of oropharyngeal cancers.⁵ The HPV 6 and 11 are also known to be responsible for 90% of genital warts. Studies have shown that out of 100 HPV types, at least 40 affect the genital tract, and

at least 15 of these are associated with cervical cancer.⁶ From this fact, developing prophylactic cervical cancer vaccines has become an important defining moment in the protection from cervical cancer. In this article, the latest status regarding HPV vaccines is discussed.

The HPV and pathogenesis. The HPV is a small, double-helical, non-enveloped deoxyribonucleic acid (DNA) virus that infects mucous surfaces and skin. The HPV genotypes can be divided into 'high-risk' and 'low-risk' groups associated with their potential to develop cervical cancer. The HPV causes a non-cytopathic, non-systemic infection that leads to cell proliferation instead of cell lysis; for this reason, the mucosal immune system plays an important role against HPV infection.⁷ Following contagion of the cervix with HPV, infectious changes occur. These changes might regress spontaneously, but also progress into low-grade cervical intraepithelial lesions (LGSIL). Most infections tend to resolve within one to 2 years after acquisition.⁸⁻¹¹ The exact percentages are not clear, but in a recent study,¹² it has been reported that most incident infections clear, without detection of CIN, ranging from 66.9% at 36 months for HPV 31 to 91.1% for HPV 59. A small variation in the 36-month proportion of incident HPV 16, 18, and 31 infections followed by a CIN 1 lesion positive for the relevant HPV type (range 16.7-18.6%), with lower risks for HPV 59 (6.4%), and HPV 33 (2.9%) was concluded.¹² Prognosis following HPV infection seems to be associated significantly with HPV type. Compared to other high-risk HPV types, HPV 16 and HPV 18 tend to show progression versus regression.¹³ The HPV 16 was reported to persist longer than other types.¹⁴ Clearance of HPV infection is also delayed in patients with HIV infection, and in patients with immunosuppression, such as transplant recipients.¹⁵ Another factor that triggers malignant transformation is that infection shows persistence.¹⁶ Persistence is defined as the detection of the same HPV type, 2 or more times with an interval between examinations. Although genital HPV infections are commonly seen in young sexually active women, a small proportion of them shows persistence, and this issue, although not exactly understood, is associated with genetic and/or environmental factors.¹⁷

The HPV is acquired mainly through sexual contact. Vertical and perinatal transmission, though, to a lesser extent, have been reported.¹⁸ The HPV's ability to establish and develop an infection depends on the reproductive capacity of the host cell. There is no nucleus in cells in the upper layer of normal cervical epithelium. There are continuously dividing cells in the suprabasal

layer; therefore these cells get infected with the virus. The HPV reaches to this layer through micro-injuries in the epithelium, and viral gene expression occurs in these cells. The duration between the onset of infection and virus release is approximately 3 weeks. The occurrence of lesions, however, shows variation from a few weeks to a few years.¹⁹

The HPV replication does not create cytolysis, or a cytopathic effect. For replication, viral proteins lead to cell death by delaying nuclear condensation. The chain of the virus entering the cell nucleus binds the DNA of the host. First the viral DNA, and then the capsid is synthesized. As the cells divide, infected cells rise to the upper layer of the tissue, and capsids are synthesized by means of late proteins of viral genomes. These viruses leave the tissue as the squamous epithelium flakes away. The point of entry of HPV into the body is the cervix, and because it does not produce viremia, the virus hides itself from the immune system, and natural immunity falls short in protection.²⁰ In the end, as there is no inflammation, there is also no signal to warn the immune system, and the immune response here is in the form of a local cellular immune response.¹⁹ The virus, which integrates into the cellular DNA in cancer and high-grade lesions, remains episomal, without being integrated into the DNA, within the cell in low-grade and other lesions. If the condition progresses (high-grade cervical intraepithelial lesions [HGSIL] and advanced lesions), viral episomal DNAs reconnect to fragile regions of the host DNA. The process of connecting to the host DNA is considered as the beginning of the course of malignant transformation.¹⁸ In the viral genome (double-helical DNA molecule), there are 8 Open Reading Frame (ORF) proteins responsible for replication, 6 being early stage (E1, E2, E3, E4, E5, E6) and 2 being late stage (L1, L2). Of these, E5, E6, and E7 play an important role in cell proliferation and survival, and particularly E6 and E7 are known to be highly crucial in HPV associated carcinogenesis.²¹ Persistent expression of E6 and E7 oncoproteins causes genetic mutations leading to cellular immortalization and consequently, malignant transformation via 2 intracellular proteins; p53 and retinoblastoma (Rb). The p53 protein functions as a tumor suppressor protein in the normal cell, and acts as a regulator of cell growth by controlling cell cycle transit from G0/G1 to the S phase. The HPV protein E6 binding to p53 causes unchecked cellular cycling, and an anti-apoptotic process induces chromosomal mutations without DNA repair. The Rb protein also inhibits positive growth regulation and induces apoptosis in response to DNA

damage. Although HPV types causing malignant transformation, and HPV types causing benign course lesions are structurally similar to one another, it is not certain which factors determine oncogenic potential. In this case, when E6 and E7 proteins of high-/low-risk HPV types are compared, it was seen that: a) low-risk E6 proteins do not stimulate p53 degradation; b) telomerase enzyme is not activated; and c) low risk E7 proteins, compared to high-risk proteins, bind the Rb protein less effectively, and do not induce Rb degradation.²¹ In light of such information, vaccines were created against different stages in the HPV growth cycle. For prophylactic vaccines the object is primary protection, whereas for therapeutic vaccines, treatment is aimed toward existent infection or neoplasia. In a recent study by Kwak et al,²² the mechanisms how the L1 virus-like particle (VLP) vaccines act, and mediate protection were discussed. The protection of neutralizing antibodies was emphasized by the passive transfer of sera from L1 VLP immunized animals to naïve animals. The role of memory B cells in latter immunization against mucosal HPV and the probable second generation HPV vaccines' mechanisms were also discussed.²²

The HPV vaccines. The HPV vaccines can be analyzed in 2 groups, the ones being developed (prophylactic), and the ones planning to be developed (therapeutic). For prophylactic vaccines, the object is to neutralize the free virus particles, and therefore, to prevent HPV contagion by triggering the production of neutralizing antibodies against capsid major and minor antigens L1 and L2. From the vaccinated person's point of view, the vaccine used should decrease one's abnormal cytology,

and risk of cancer development. The HPV VLP vaccine clinical studies are being conducted with 2 HPV vaccines; Gardasil® (Merck & Co Inc, Whitehouse Station, NJ, USA) and Cervarix™ (Glaxo-SmithKline Biologicals, Rixensart, Belgium). Both HPV vaccines contain HPV L1 protein, however, they have different valences and adjuvants. Cervarix™ has been developed against HPV 16 and 18 infections (bivalent). With Gardasil®, protection against HPV 6 and HPV 11, infections is targeted in addition to HPV 16 and 18 (quadrivalent).²³ The US Food & Drug Administration (FDA) granted approval in June 2006 for Gardasil® to be used in women aged between 9-26 years against cervical, vulvar, vaginal, and anal cancers caused by HPV 16 and 18; condyloma acuminatum caused by HPV 6 and 11; CIN 1-3; cervical adenocarcinoma in situ; vulvar intraepithelial neoplasia ([VIN] 2, 3); vaginal intraepithelial neoplasia ([VAIN] 2, 3), and anal intraepithelial neoplasia ([AIN] 1, 2, 3) caused by HPV 6, 11, 16, and 18. Gardasil® was approved for males, 9 through 26 years of age for the prevention of genital warts, and the FDA added the indication for prevention of anal cancer in females and males in December 2010. The indications and usage of the quadrivalent vaccine in males are as follows: anal cancer caused by HPV types 16 and 18; genital warts (condyloma acuminatum) caused by HPV types 6 and 11; and AIN grades 1, 2, and 3 caused by HPV types 6, 11, 16, and 18.²⁴ Cervarix™ was approved in October 2009 for protection against cervical cancer, CIN 1, 2 and higher grade lesions, and cervical adenocarcinoma in situ in females 9-26 years of age.²⁵ Usage properties, content and application schemes of currently used bivalent and quadrivalent vaccines are shown in detail in Table 1.

Table 1 - Properties of prophylactic vaccines.²³⁻²⁵

Variables	Cervarix™ Bivalent vaccine	Gardasil® Quadrivalent vaccine
Active content	HPV 16 L1 protein (20 mcg) HPV 18 L1 protein (20 mcg)	HPV 6 L1 protein (20 mcg) HPV 11 L1 protein (40 mcg) HPV 16 L1 protein (40 mcg) HPV 18 L1 protein (20 mcg)
Adjuvant	500 µg aluminium hydroxide with 50 µg 3-O-deacylated-4'-monophosphoril lipid A (ASO ₄)	225 µg aluminium hydroxyphosphate sulfate
Production	Baculovirus	Fermented
Dose and application	0.5 ml intramuscular, 0, 1, 6 months, deltoid region	0.5 ml intramuscular, 0, 2, 6 months, deltoid or foreleg anterolateral
Clinical efficiency	Cervical cancer CIN 1, 2 and higher grade lesions Cervical adenocarcinoma in situ	HGSIL High-grade vulvar lesion (VIN 2 and VIN3) HPV 6, 11, 16, 18 associated genital warts Vaginal and anal cancer and pre-cancer lesions

HPV - human papillomavirus; L1 - late stage 1; CIN - cervical intraepithelial neoplasia;
HGSIL - high-grade cervical intraepithelial lesions; VIN - vulvar intraepithelial neoplasia

Cervical cancer is the first cancer that has been related to a virus. For the development of cervical cancer, in most cases, the presence of HPV infection is mandatory. Up to 57.4% of cervical cancer cases were associated with HPV 16, and 16.6% with HPV 18. Single or multiple infections with the 2 types were detected in 74% of all cases.⁶ In a study²⁶ with 10,575 cases of invasive cervical cancer, 85% were positive for HPV DNA, and HPV 16 and 18 were detected in 71% of all invasive cervical cancer cases. Geographic variation was also seen that the highest prevalence of HPV 16 was observed in ratios of 69.7 in Europe/North America, and 67.6 % in North Africa.⁶

In studies with infected rabbits and dogs, it has been shown that serum antibody response occurred against viral capsid proteins, and seropositive animals were protected for their lifetime against high dose virus inoculation.⁵ Neutralizing serum antibody response is in direct relation to the L1 capsid protein. Despite HPV antibodies being type specific, it has been shown that in those, in which an immune response occurs with a bivalent vaccine, protection is achieved also against HPV 31, 33, and 45 by cross-reactivity, although the mechanism is not clearly understood.²⁷ In a recent study by Kemp et al,²⁸ it has been shown that with 3 doses of bivalent HPV vaccine, there was an evident increase in serum titers for HPV 31 and 45 in the 12-month follow-up of patients. However, it has been confirmed that considering HPV 16 and HPV 18 antibody levels, neutralizing antibody titers against HPV 31 and HPV 45 were 100 times lower. It has been reported that in time, depending on the decrease in neutralizing antibody titers against HPV 31 and HPV 45, the efficiency of the vaccine decreased, with effectiveness of 79% for HPV 31, and 76% for HPV 45. In the same study,²⁸ antibody titers for HPV 33 were not measured due to the absence of an appropriate pseudovirion. With its potential effects shown in a randomized, double blind, placebo-controlled phase-II study of quadrivalent vaccine conducted on 502 women in 2005,²⁹ a more comprehensive international phase-III, multi-national, prospective, placebo-controlled study was planned.³⁰ A total of 12,167 women aged 15-26 were randomly assigned to receive 3 doses of quadrivalent HPV vaccine or placebo. The patients who did not have any evidence of HPV 16 and HPV 18 infection through one month after the application of 3 doses of vaccine were referred to as 'HPV-naïve'. The end-points were CIN 2 or 3, adenocarcinoma in situ, or cervical cancer associated with HPV 16 or 18 among 'HPV-naïve' patients. This study has the distinction of being the

first and most comprehensive study on showing the effect of VLP vaccine in protecting against high-grade CIN (FUTURE II study group 2007). The results of this study demonstrated that vaccine efficacy among 'HPV-naïve' patients was 98% for the prevention of the end-point. It has been reported in the results of the conducted study that VLP vaccines were highly efficient in lower genital tract neoplasia specific to type 16 and 18, while quadrivalent vaccine provided protection against genital warts. But one point should be emphasized; that vaccine efficacy for CIN 2 or 3 related to all types of HPV was significantly lower in the overall population of women, in which the population consists of baseline or incident HPV infections by one month after the last dose of vaccine (44%).³⁰

The FUTURE I trial, in which the quadrivalent vaccine's efficacy on anogenital warts, VIN or VAIN grades 1-3, or cancer associated with HPV 6, 11, 16, 18 lesions aimed to be detected, demonstrated 100% of effectiveness in preventing anogenital diseases in 'HPV-naïve' women.³¹ While HPV vaccination does not reduce progression to cervical pre-cancer lesions in women with ongoing infections at the time of vaccination, the effect of vaccination in preventing subsequent disease after treatment was evaluated in a retrospective pooled analysis of the 2 FUTURE trials.³² The women with cervical and vulvar diseases despite vaccination were reported to have a lower incidence of subsequent CIN grade 2, or worse when compared with placebo recipients. The authors concluded that previous vaccination with quadrivalent HPV vaccine among women who had surgical treatment for HPV related disease significantly reduced the incidence of subsequent HPV related disease, including high-grade disease.³² As it was the first study that evaluated the efficiency of the vaccine on over 25-year-old patients, the study by Munoz et al³³ is distinct. The results showed that the quadrivalent vaccine had a protective property in older patients. Nevertheless, it was indicated that comprehensive studies requiring long-term follow-up were needed.³³

In the phase-II study, in which a bivalent vaccine was researched, it has been stated that protection against HPV 16 and 18 was 91.6%, and protection against cytologic anomaly was over 90%.³⁴ In a study, in which the average follow-up time reached 47 months, and long-term efficiency and immunogenicity were assessed, the percentage of protection against type 16 and 18 was determined to be 96%, and the percentage of protection against cytologic anomalies associated with these was confirmed to be the same.³⁵ Seroconversion

was determined to be 98% in the 4.5-year period that followed vaccination. Protection against HPV 31 and 45 infections was also detected, and it was reported that this situation might have originated from the phylogenetic connection of HPV 16 and 18 with HPV 31 and 45.³⁵ The bivalent vaccine was evaluated in one large, phase-III, double-blind, placebo-controlled trial called PATRICIA (Papilloma Trial Against Cancer in Young Adults), and an autonomous US National Cancer Institute (NCI)-sponsored trial in Costa Rica was designed to investigate the efficacy and population impact of the bivalent vaccine in the prevention of cervical cancer precursors.^{36,37} A total of 18,644 women between 15 and 25 years of age were included, and the bivalent vaccination scheme was applied in PATRICIA. The efficiency of the vaccine against CIN 2 lesions associated with HPV 16 and 18 was found to be 92.2% in the 35-month follow-up period after the last dose of vaccine.³⁶ Again, intention-to-treat analysis of the vaccine efficacy was significantly lower in the overall population for CIN 2, or more severe disease (30%).³⁶

The response time of antibodies against VLP and the long-term efficiency of protection in the subsequent years for HPV vaccines is not yet known for certain. The VLP antibodies reach maximum titer in the seventh month, blood levels decrease until approximately 24 months later, and then they become stabilized.²⁹ Antibody titers measured in the third year were comparable or higher than those of natural infection with the application of Gardasil®.³⁸ The efficacy of Gardasil was determined (90%; 95% confidence interval [CI]: 71.97) in the prevention of persistent infection or disease, 3 years after the first dose.²⁹ In a phase III, double-blind, placebo-controlled trial evaluating the efficacy of Gardasil® in women aged 24-45 years, in a mean follow-up duration of 2.2 years noted a 91% efficacy (95% CI) in the per-protocol susceptible population.³³ Comparable results (long-term efficacy,

high, and sustained immunogenicity, and favorable safety) were also detected for Cervarix™ after 6.4 years of follow-up.³⁹ Among all these data, we still do not have knowledge of the duration of protection after the immunization period. A summary of detailed results from the 3 major studies on HPV vaccines is presented in Table 2.

The HPV vaccine applications. In countries where HPV vaccine application is planned, target groups involve differences in terms of age, application model, and patient follow-up. Although it is known that acceptance and application of HPV vaccines is especially high in Western countries, it is evident that the situation is different in developing countries. Among the reasons for this situation are vaccine cost, awareness of the disease, lack of public information, and state policies. Assessments regarding the age range, in which the vaccine should be applied are in line with the studies conducted. In accordance with the recommendations of the Turkish Cervical Cancer Work Group, the age range in which the effect of vaccine on the immune response would be best was determined to be 11-12, considering that it should be before the beginning of sexual activity.⁴⁰ The immune response prominence, especially before 12 years of age, and the permanence of the response shows the importance of the application in this age range. The HPV infections leading to cervical cancer contaminate sexually, and HPV infections are monitored in young adults mostly after sexual activity. Therefore, the object in vaccination programs is to perform the vaccination before sexual debut. At this point, the recommendation of the Turkish Cervical Cancer Work Group is catch-up vaccination for girls and women aged 13-26 years, who were previously not vaccinated, or did not complete their vaccination series.⁴⁰ The best is to perform the vaccination before the probability of exposure to HPV through sexual contact.⁴¹ Various expert guideline committees have made some recommendations for the

Table 2 - Efficiency results of 3 major studies conducted on human papillomavirus (HPV) virus-like particle (VLP) vaccines (all randomized cases regardless of HPV condition).

Study	Total number of cases	End-point	Percent vaccine efficiency (95% CI)
Future II Quadrivalent and placebo ³⁰	10,565*	CIN2+	98 (86-100)
PATRICIA Bivalent and HepA (control) ³⁶	14,656*	CIN2+ (16/18)	92.9 (79.9-98.3)
Future I Quadrivalent and placebo ³¹	4,540*	VIN2+/VAIN2+ Genital warts	100 (49-100) 100 (92-100)

*Cases belonging to the per-protocol susceptible group (the group that was HPV DNA negative, seronegative prior to vaccination, and vaccinated with 3 doses). PATRICIA - Papilloma Trial Against Cancer in Young Adults; HepA - Hepatitis A; CIN - cervical intraepithelial neoplasia; CI - confidence interval

use of HPV vaccines in females. The American Academy of Pediatrics (AAP) recommended immunization against HPV for all 11-12 year-old children. According to the recommendation, girls 11-12 years of age should be immunized routinely with 3 doses of either with quadrivalent, or bivalent HPV vaccine.⁴² Boys 11-12 years of age should be immunized with 3 doses of quadrivalent HPV vaccine. The vaccines can be administered starting at 9 years of age for both girls and boys according to physician preferences.⁴² The American Cancer Society recommends HPV vaccination of females between the ages of 11 and 18 years, and does not recommend 'catch up' vaccination between 19-26 years of age.⁴³ The Advisory Committee on Immunization Practices (ACIP) recommends routinely the use of bivalent or quadrivalent HPV vaccines in 11 and 12 year-old females for the prevention of CIN and cervical cancer, and quadrivalent HPV vaccine for the prevention of AIN and anal cancer.⁴⁴ In contrast to these data, Tomljenovic & Shaw⁴⁵ did not advise HPV vaccination routinely and stated that physicians should adopt a more rigorous evidence-based medicine approach to provide an objective evaluation of vaccine risks and benefits.

Performing the vaccination on men, although controversial, has been granted approval in some countries, such as Australia, Mexico, United Kingdom, and the US. According to AAP recommendations all boys and men 13 through 21 years of age who have not been immunized previously should receive the quadrivalent HPV vaccine.⁴² The ACIP recommends the use of quadrivalent vaccine in males aged 11 or 12 years.⁴⁶ The guidance that the quadrivalent vaccine might be given to males aged 9 through 26 years in 2009 by ACIP was replaced with recommendations on October 25, 2011.⁴⁶ The 'catch up' protocol was also recommended between the ages of 13 through 21 by the same committee. There is information regarding the vaccine protecting men against HPV associated anogenital, and head and neck cancers, and preventing male-to-female or male-to-male mediated viral transmission.⁴⁷ The basic argument on this issue is based on cost effectiveness. However, studies have shown that the models, in which women and men are vaccinated together are more cost effective, than those in which only women are vaccinated.⁴⁷ Regarding the issue, as women are vaccinated and informed, informing men also regarding protection from HPV infections, HPV means of transmission, morbidity and mortality, should be the fundamental policy. The point that should be emphasized is that of optimal timing of

HPV immunization for both women and men is before the onset of sexual activity.

The HPV vaccination and pregnancy. Studies on vertical and horizontal transmission of HPV from mothers to infants, and HPV infection and persistence in neonates are conflicting.⁴⁸ In the literature, preterm delivery⁴⁹ and spontaneous abortion⁵⁰ were reported, but no true cause effect was found. Inversely, vertical transmission of HPV was found to be lower; among HPV DNA(+) mothers, 3% of their infants were DNA (+), and this ratio was detected 0.8% in HPV DNA (-) mothers.⁵¹ Moreover, HPV infection has not been associated with an increased risk of birth defects. Both HPV vaccines are inactive recombinant vaccines. Even though the HPV vaccine has not been associated with adverse pregnancy outcomes, and the FDA designated the pregnancy category of the HPV vaccine as 'B', there is consensus not to perform HPV vaccination during pregnancy.⁴⁰ If a vaccination protocol was initiated prior to pregnancy, and the first 2 doses were given but not completed, the third dose of the vaccine should not be given, as not enough studies have been conducted on humans. The remaining dose of vaccine should be scheduled in a period of time not longer than a year. If only the first dose of vaccine was given, the whole course of vaccine should be initiated, starting from the first dose after delivery.⁴⁰ If a woman has received any HPV vaccines and is planning to become pregnant, she may be informed that there is no need to delay pregnancy.⁵²

Therapeutic vaccine applications. The purpose of therapeutic vaccines should be inducing and triggering HPV T-cell mediated immunity, if it is weakened, or does not function in a natural way. There are therapeutic HPV 16 vaccines being tested. Percentages of inducing E6, E7 immunity of these vaccines has shown differences in the conducted studies. Although immunogenicity and reliability of therapeutic vaccines have been shown in early phase clinical studies performed on cervical cancer patients, their clinical effects have not yet been presented. This condition results from the immunologic escape mechanisms that the cervical tumor produces during its growth.⁵³ It is obvious that, in terms of efficiency, reliability and cost, more comprehensive studies on this subject are needed.

In conclusion, with the present data, administering prophylactic vaccines in preventing cervical cancer seems appropriate. The importance of timing of the vaccination before sexual debut and in the period, in which the immune response is the highest should be emphasized, and at the same time it should be kept in mind that it is also efficient in sexually active young

women, and in advanced ages as well. Since HPV 16 and 18 play a major role in the etiology during the development of cervical cancer, and HPV vaccination neither treats nor protects against pre-existing HPV infections, the value of cervical cancer screening is of great importance. Considering this information, the participation in cervical cancer screening programs also for those who have been vaccinated should be ensured.

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References

- GLOBOCAN 2002. Cancer Incidence, Mortality and Prevalence Worldwide. Lyon (France): IARC Press; 2001.
- Tuncer S, Ustaçelebi S. Detection of Human Papilloma virus Type 16 and 18 by polymerase chain reaction in cervical biopsy samples. *Flora* 1996; 1: 40-44. Available from URL: http://www.floradergisi.org/abstracttext.aspx?issue_id=50&ref_ind_id=8
- Castellsagué X, Schneider A, Kaufmann AM, Bosch FX. HPV vaccination against cervical cancer in women above 25 years of age: key considerations and perspectives. *Gynecol Oncol* 2009; 115 (Suppl 3): S15-S23.
- Hoots BE, Palefsky JM, Pimenta JM, Smith JS. Human papillomavirus type distribution in anal cancer and anal intraepithelial lesions. *Int J Cancer* 2009; 124: 2375-2383.
- Stanley MA. Prophylactic HPV vaccines: pre-clinical and proof of principle studies. In: Stern LP, Kitchener HC, editors. Vaccines for the Prevention of Cervical Cancer. New York (NY): Oxford University Press; 2010. p. 67-76. Available from URL: <http://www.oup.com/us/catalog/general/subject/Medicine/Oncology/?view=usa&sf=toc&ci=9780199588633>
- Muñoz N, Bosch FX, Castellsagué X, Diaz M, de Sanjose S, Hammouda D, et al. Against which human papillomavirus types shall we vaccinate and screen? The international perspective. *Int J Cancer* 2004; 111: 278-285.
- Williamson AL, Passmore JA, Rybicki EP. Strategies for the prevention of cervical cancer by human papillomavirus vaccination. *Best Pract Res Clin Obstet Gynaecol* 2005; 19: 531-544.
- Insinga RP, Perez G, Wheeler CM, Koutsky LA, Garland SM, Leodolter S, et al. Incidence, duration, and reappearance of type-specific cervical human papillomavirus infections in young women. *Cancer Epidemiol Biomarkers Prev* 2010; 19: 1585-1594.
- Gravitt PE. The known unknowns of HPV natural history. *J Clin Invest* 2011; 121: 4593-4599.
- Woodman CB, Collins S, Winter H, Bailey A, Ellis J, Prior P, et al. Natural history of cervical human papillomavirus infection in young women: a longitudinal cohort study. *Lancet* 2001; 357: 1831-1836.
- Moscicki AB, Schiffman M, Kjaer S, Villa LL. Chapter 5: Updating the natural history of HPV and anogenital cancer. *Vaccine* 2006; 24 (Supp 3): S42-S51.
- Insinga RP, Perez G, Wheeler CM, Koutsky LA, Garland SM, Leodolter S, et al. Incident cervical HPV infections in young women: transition probabilities for CIN and infection clearance. *Cancer Epidemiol Biomarkers Prev* 2011; 20: 287-296.
- Bosch FX, Burchell AN, Schiffman M, Giuliano AR, de Sanjose S, Bruni L, et al. Epidemiology and natural history of human papillomavirus infections and type-specific implications in cervical neoplasia. *Vaccine* 2008; 26 (Supp 10): K1-K16.
- Schiffman M, Herrero R, Desalle R, Hildesheim A, Wacholder S, Rodriguez AC, et al. The carcinogenicity of human papillomavirus types reflects viral evolution. *Virology* 2005; 337: 76-84.
- Frazer IH, Leggatt GR, Mattarollo SR. Prevention and treatment of papillomavirus-related cancers through immunization. *Annu Rev Immunol* 2011; 29: 111-138.
- Kjaer SK, van den Brule AJ, Paull G, Svare EI, Sherman ME, Thomsen BL, et al. Type specific persistence of high risk human papillomavirus (HPV) as indicator of high grade cervical squamous intraepithelial lesions in young women: population based prospective follow up study. *BMJ* 2002; 325: 572.
- Garland SM, Smith JS. Human papillomavirus vaccines current status and future prospects. *Drugs* 2010; 70: 1079-1098.
- Bosch FX, Qiao YL, Castellsagué X. The epidemiology of human papillomavirus infection and its association with cervical cancer. *Int J Gynecol Obstet* 2006; 94 (Supp 1): S8-S21.
- Stanley M. Immune responses to human papillomavirus. *Vaccine* 2006; 24 (Suppl 1): S16-S22.
- Viscidi RP, Schiffman M, Hildesheim A, Herrero R, Castle PE, Bratti MC, et al. Seroactivity to human papillomavirus (HPV) types 16, 18, or 31 and risk of subsequent HPV infection: results from a population-based study in Costa Rica. *Cancer Epidemiol Biomarkers Prev* 2004; 13: 324-327.
- Roberts S, Young LS. Role of HPV in cervical carcinogenesis. In: Stern LP, Kitchener HC, editors. Vaccines for the Prevention of Cervical Cancer. New York (NY): Oxford University Press; 2010. p. 25-33. Available from URL: <http://www.oup.com/us/catalog/general/subject/Medicine/Oncology/?view=usa&sf=toc&ci=9780199588633>
- Kwak K, Yemelyanova A, Roden RBS. Prevention of cancer by prophylactic human papillomavirus vaccines. *Curr Opin Immunol* 2011; 23: 244-251.
- Kitchener HC. Prophylactic HPV vaccination: current status. In: Stern LP, Kitchener HC, editors. Vaccines for the Prevention of Cervical Cancer. New York (NY): Oxford University Press; 2010. p. 77-90.
- Food and Drug Administration. Highlights of prescribing information. Gardasil (human papillomavirus quadrivalent [types 6, 11, 16 and 18]). Silver Spring (MD): Food and Drug Administration; 2011. [Accessed 23 August 2012] Available from URL: <http://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm111263.pdf>
- GlaxoSmithKline. Cervarix Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant (Glaxo-SmithKline Biologicals, Rixensart, Belgium) Prescribing Information. Highlights of Prescribing Information. Revised 01/2011. [Accessed 03 March 2011. Updated 2012 August]. Available from URL: http://us.gsk.com/products/assets/us_cervarix.pdf
- de Sanjose S, Quint WG, Alemany L, Geraets DT, Klaustermeier JE, Lloveras B, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. *Lancet Oncol* 2010; 11: 1048-1056.

27. Jenkins D. A review of cross-protection against oncogenic HPV by an HPV-16/18 ASO4- adjuvanted cervical cancer vaccine: importance of virological and clinical endpoints and implications for mass vaccination in cervical cancer prevention. *Gynecol Oncol* 2008; 110 (Supp 1): S18-S25.
28. Kemp TJ, Hildesheim A, Safaeian M, Dauner JG, Pan Y, Porras C, et al. HPV16/18 L1 VLP vaccine induces cross-neutralizing antibodies that may mediate cross-protection. *Vaccine* 2011; 29: 2011-2014.
29. Villa LL, Costa RL, Petta CA, Andrade RP, Ault KA, Giuliano AR, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomized double-blind placebo-controlled multicenter phase II efficacy trial. *Lancet Oncol* 2005; 6: 271-278.
30. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 2007; 356: 1915-1927.
31. Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, Harper DM, Leodolter S, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med*. 2007; 356: 1928-1943.
32. Joura EA, Garland SM, Paavonen J, Ferris DG, Perez G, Ault KA, et al. Effect of the human papillomavirus (HPV) quadrivalent vaccine in a subgroup of women with cervical and vulvar disease: retrospective pooled analysis of trial data. *BMJ* 2012; 344: 1401.
33. Muñoz N, Manalastas R Jr, Pitisuttithum P, Tresukosol D, Monsonogo J, Ault K, et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women ages 24-45 years: a randomised, double-blind trial. *Lancet* 2009; 373: 1949-1957.
34. Harper DM, Franco EL, Wheeler C, Ferris DG, Jenkins D, Schuid A, et al. GlaxoSmithKline HPV Vaccine Study Group. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papilloma virus types 16 and 18 in young women: a randomised controlled trial. *Lancet* 2004; 364: 1757-1765.
35. Harper DM, Franco EL, Wheeler C, Moscicki AB, Romanowski B, Roteli-Martins CM, et al. GlaxoSmithKline HPV Vaccine Study Group. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papilloma virus types 16 and 18: follow-up from a randomised controlled trial. *Lancet* 2006; 367: 1247-1255.
36. Paavonen J, Naud P, Salmeron J, Wheeler CM, Chow SN, Apter D, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04- adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet* 2009; 374: 301-314.
37. Herrero R, Hildesheim A, Rodriguez AC, Wacholder S, Bratti C, Solomon D, et al. Rationale and design of a community-based double-blind randomized clinical trial of an HPV 16 and 18 vaccine in Guanacaste, Costa Rica. *Vaccine* 2008; 26: 4795-4808.
38. Villa LL, Ault KA, Giuliano AR, Costa RL, Petta CA, Andrade RP, et al. Immunologic responses following administration of a vaccine targeting human papillomavirus Types 6, 11, 16, and 18. *Vaccine* 2006; 24: 5571-5583.
39. GlaxoSmithKline Vaccine HPV-007 Study Group, Romanowski B, de Borja PC, Naud PS, Roteli-Martins CM, De Carvalho NS, Teixeira JC, et al. Sustained efficacy and immunogenicity of the human papillomavirus (HPV)-16/18 AS04- adjuvanted vaccine: analysis of a randomised placebo-controlled trial up to 6.4 years. *Lancet* 2009; 374: 1975-1985.
40. Boswell S. Serviks kanseri aşılmasıyla ilgili Türk Servikal Kanser Çalışma Grubunun önerileri. *The Turkish Journal of Gynecologic Oncology* 2010; 13: 51-54. Available from URL: http://trsgo.dergisi.org/pdf/pdf_TRSGO_139.pdf
41. Schiller JT, Castellsague X, Villa LL, Hildesheim A. An update of prophylactic human papillomavirus L1 virus-like particle vaccine clinical trial results. *Vaccine* 2008; 26 (Supp 10): K53-K61.
42. Committee on Infectious Diseases. HPV Vaccine Recommendations. *Pediatrics* 2012; 129: 602-605.
43. Saslow D, Castle PE, Cox JT, Davey DD, Einstein MH, Ferris DG, et al. American Cancer Society Guideline for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors. *CA Cancer J Clin* 2007; 57: 7-28.
44. Advisory Committee on Immunization Practices. Recommended adult immunization schedule: United States, 2010. *Ann Intern Med* 2010; 152: 36-39.
45. Tomljenovic L, Shaw CA. Human papillomavirus (HPV) vaccine policy and evidence-based medicine: Are they at odds? *Ann Med* 2011 Dec 22 [Epub ahead of print].
46. Centers for Disease Control and Prevention (CDC). Recommendations on the use of quadrivalent human papillomavirus vaccine in males-Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR Morb Mortal Wkly Rep* 2011; 60: 1705-1708.
47. Zimet GD, Rosenthal SL. HPV vaccine and males: Issues and challenges. *Gynecol Oncol* 2010; 117: S26-S31.
48. Cason J, Mant CA. High-risk mucosal human papillomavirus infections during infancy & childhood. *J Clin Virol* 2005; 32 (Supp 1): S52-S58.
49. Gomez LM, Ma Y, Ho C, McGrath CM, Nelson DB, Parry S. Placental infection with human papillomavirus is associated with spontaneous preterm delivery. *Hum Reprod* 2008; 23: 709-715.
50. Hermonat PL, Kechelava S, Lowery CL, Korourian S. Trophoblasts are the preferential target for human papilloma virus infection in spontaneously aborted products of conception. *Hum Pathol* 1998; 29: 170-174.
51. Smith EM, Parker MA, Rubenstein LM, Haugen TH, Hamsikova E, Turek LP. Evidence for vertical transmission from mothers to infants. *Infect Dis Obstet Gynecol* 2010; 2010: 326369.
52. Narducci A, Einarson A, Bozzo P. Human papillomavirus vaccine and pregnancy. *Can Fam Physician* 2012; 58: 268-269.
53. van der Burg SH. Therapeutic HPV vaccines. In: Stern LP, Kitchener HC, editors. Vaccines for the Prevention of Cervical Cancer. New York (NY): Oxford University Press; 2010. p. 133-144.