Human papilloma virus in adolescence

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Summary

Human papilloma virus (HPV) is one of the most widespread sexually transmitted diseases especially in adolescence. The majority of the infections are self-sustained by the immune system. However, HPV may lead to genital warts, cervical dysplasia and cervical cancer. Sexually active adolescent females should be encouraged to obtain gynecologic screening for HPV and be well informed about HPV and the risks associated with this infection. All the efforts are now focused on the vaccines that are being developed to reduce the morbidity and mortality associated with HPV infection if administered in time.

Key words: HPV infection; Adolescence; Teenager; Cervical lesions; Prevention; Treatment.

Introduction

Human papilloma virus (HPV), one of the most widespread sexually transmitted diseases, particularly in adolescence, has a prevalence of 30% to 50% among sexually active young women [1]. Although the majority of the infections self-sustain automatically, it may conduct to clinical sequelae such as anogenital condylomata and cervical squamous cell carcinomas with high morbidity and mortality rates. A lot of initiatives have been conducted in order to inform young people about HPV, its implications and how they can protect themselves from acquiring and transmitting the disease.

Biology, epidemiology and transmission of HPV

Human papilloma virus is a small non-enveloped DNA virus, with icosahedra structure. Its genome contains two regions, one early E region and one late L region. More than 80 types of HPV have been identified, 30 of which are known to affect the genital tract [2]. They are divided into low-risk types including HPV 6,11,40,42,44,54, associated with genital warts and into high-risk types including 16-like (16,31,33,35,52,58,67), 18-like (18,26,39,45,59,68,70,69,51) and 56-like (53,56,66) associated with high risk for oncogenesis [3]. HPV infects basal epithelial cells [1]. After the viral infection, the epithelial cells in most samples from adolescents are characterized by large, hyperchromatic, often bizarre shaped nuclei. The most important cytopathic effect on the cervical squamous epithelium caused by HPV infection is the presence of koilocytes in cervical biopsies, which are mostly seen in the lower epithelial layers in young women compared to the common presence of koilocytes in the upper layers in older females [4].

Human papilloma virus is one of the most common sexually transmitted diseases among adolescents. In the United States it is estimated that 20 million Americans have HPV infection and 5.5 million new cases are diagnosed every year [5]. Epidemiologic studies suggest that the cumulative risk for someone to acquire HPV infection during his lifetime is approximately 79% [6]. Moscicki *et al.*, found in a study of adolescents who were initially HPV negative that 55% of them acquired HPV within three years [7]. Fifty percent of all the reported sexually transmitted diseases occur among adolescents, although they represent only 25% of the sexually active population [8].

HPV is transmitted by skin to skin contact. For full infection it is important that the virus gets access to basal cells through tears, in the squamous or mucosal epithelium, that are often produced by sexual activity. Cervical infection, almost in all cases, requires sexual intercourse but HPV can be transmitted without sexual intercourse by skin to skin contact, using fingers, sex toys or even tampons [9]. Indeed, different forms of sexual behavior may lead sexually inactive adolescents to HPV infection in other parts of the anogenital area [10]. HPV can also be transmitted to neonates from their mothers during vaginal delivery resulting in recurrent respiratory papillomatosis (RRP) which may be fatal for the neonate [8].

Risk factors for acquiring HPV

It is reported that HPV infection is more common in adolescents than in adult women [11]. A lot of reasons can explain this difference. First of all, the cervix in adolescents is more vulnerable to HPV infection due to the physiological immaturity [1, 12]. It is covered by columnar epithelium [13] giving the cervix a scarlet, velvet appearance [6]. Adolescent menarche is characterized by anovulatory menstrual cycles due to a lack of cyclic progesterone secretion leading to inadequate production of

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cervical mucus which acts as a protective barrier against infectious agents [1]. In addition their cervix is characterized by a large area of immature columnar and metaplastic cells on the ectocervix, referred to as ectopy. This area is very vulnerable to sexually transmitted infections such as HPV, Chlamydia trachomatis and HIV. The immaturity of adolescent cervices leads to HPV infection by two other mechanisms such as the rapid rate of metaplastic change and the incompletely developed immune responses [1]. There are also cervical cell membrane differences that allow enhanced interaction between infecting virus and target cells. Thus, it is very easy to understand why HPV is most common in sexually active women younger than 25 years old.

There are not only the biological mechanisms that make adolescents more vulnerable to HPV infection but also their sexual behavior plays an important role too. Epidemiologic studies have supported the link between sexual activity and acquisition of HPV infection. They underscore the role of early age of first sexual intercourse and the number of sexual partners [14]. Higher risks of HPV infection also affect young women who practice risky sexual behaviors under the influence of alcohol and illicit drugs [1]. The history of other sexually transmitted infections, such as genital warts or herpes simplex virus (HSV), plays an important role as well, because these factors cause inflammation and breaks in the epithelium barrier allowing HPV direct access to basic epithelial cells [8, 15]. Unlike Chlamydia trachomatis or other sexually transmitted diseases, use of condoms is not highly effective in reducing HPV, because when the virus is present it involves almost the whole genital area [6].

Clinical implications of HPV infection

The majority of HPV infections in adolescents are occult or asymptomatic [16]. It has been reported that over 90% of them are cleared by the immune system [8]. However, the majority of chronic infections are associated with cancer in women. Low-risk HPV types are the cause of benign lesions, including anogenital condylomata and low-grade genital abnormalities, but are not found in genital cancers. High-risk HPV types cause precancerous and cancerous lesions of the cervix. HPV is also a very important etiologic factor for vaginal, vulvar, penile and anal cancers, and has been associated with pharyngeal and skin cancer [8].

Cervical cancer is the second most common cancer in women worldwide, following breast cancer [5]. It is reported that, more than 500,000 new cases are contracted each year, most commonly found in middle-aged or older women [6, 8]. Cervical cancer has proven to be the result of a chronic, progressive cellular transformation and HPV is the primary causative factor in this process [6]. Epidemiologic studies have shown that HPV is a necessary but not sufficient factor in initiating the transformation that leads to cervical intraepithelial neoplasia (CIN) and to cancer [6]. There are a lot of cofactors in this process. The virus needs to be a persistent high-risk HPV type [8]. Most likely to persist is HPV 16 which is considered to be responsible for 40% to 60% of invasive cancers worldwide. It has been shown that HGSIL after a persistent HPV infection leads to cervical cancer within two years and that the incubation period from initial HPV infection to carcinoma in situ is approximately seven to 12 years [8].

Prospective studies demonstrate that HPV infected women do not all progress to cervical cancer, but that the lesions persist or regress [6]. It is important to identify all the biological co-factors that increase cell transformation and begin the oncogenic process because HPV is easily acquired. Early age of initiating sexual activity, high number of sexual partners and early age of parity lead to increased risk of acquiring HPV [6]. Apart from the risky sexual behavior, immunosuppression seems to be a significant co-factor for cervical cancer. This is proven by the high rate of HPV and cervical carcinoma in transplant patients or patients on chemotherapy [6]. In HIV-infected girls HPV not only is more common but is also persistent due to CD4 immunosuppression (the lower CD4 cell count, the more likely HPV persists) [3] and as it is known, persistent infection is characterized by a greater risk of developing a high-grade squamous intraepithelial lesion (HGSIL) and cervical cancer. The condition of the immune system is very important when talking about adolescents concerning acquisition of HPV and its persistence because their general health is often compromised by behaviors impacting the immune system, such as poor diet and smoking.

Smoking is an important risk factor for invasive cervical cancer [17]. It has a negative affect on the immune system and as a fact, smokers become more vulnerable to infections such as HPV [6, 8, 11, 14, 18]. Several studies have shown that increased risk for precancerous and cancerous lesions also have been noticed in women with high parity (more than three pregnancies) [6], prolonged use of oral contraceptives [19], remarkable alcohol consumption, uncircumcised male partner and history of infection with HSV or Chlamydia trachomatis [8].

Screening and treatment guidelines for adolescents

A 70% reduction in the incidence of cervical cancer has been reported in the United States over the last five decades as a result of the introduction of the Papanicolaou (Pap) smear as a routine screening program [16]. According to the American Cancer Society women should begin cervical screening three years after the initiation of sexual activity or at 21 years of age, whichever comes first [20]. Screening should take place every year with traditional cytology (Papanicolaou smears). After three normal tests, screening should take place every two years. At the age of 30, women can reduce cytologies to one every two or three years provided they do not have abnormal pap tests or other risk factors such as immunosuppression. Women over 30 are now able to have a HPV DNA test as a primary screening test but its utility in adolescents has not been proven yet because at this age a lot of girls are HPV positive [8, 17].

The American College of Obstetricians and Gynecolo-

gists (ACOG) and the American Cancer Society (ACS) have recently published evidence-based guidelines that cover a variety of issues regarding cervical cancer screening especially in adolescence. Among adolescents, cytology is usually positive for HPV and the majority of pathology is a low-grade (LG) SIL. Few adolescents have HGSIL or cervical cancer [9]. These new guidelines allow cytological LGSIL to be followed by repeat cytology in six months or by a HPV DNA test in 12 months. If the repeat cytology is normal a second cytology should be done in six months. If a diagnosis of ASCUS or greater is the result of the repeat cytology, colposcopy is recommended. On the other hand, HPV DNA testing can be performed 12 months after the LGSIL diagnosis. If the test is positive for high-risk HPV type the adolescent should be referred for colposcopy. Adolescent progression from LGSIL to HGSIL is really low, thus using repeated cytologies or HPV DNA tests for monitoring LGSIL is more preferred than colposcopy. Consequently, for CIN 1, observation is the preferred method of treatment. When cervical dysplasia is suspected in an adolescent, colposcopy is recommended. Adolescents with HGSIL and possibly persistent LGSIL need more aggressive procedures such as cryotherapy and the loop electrical excision procedure (LEEP). Physicians should be very careful when they decide to do laser cone treatments or LEEP because these have been found to increase the risk of preterm delivery [21]. All these strategies are referred to non-immunosuppressed adolescents. Teenagers with impaired cellular immunities need closer monitoring for the development of HPV-related lesions. Further studies are needed to define the most appropriate screening strategies for adolescents [8, 9, 11, 16, 22-25].

Prevention of HPV infection

Many courses of action can be taken to prevent adolescents from acquiring HPV. Primary prevention is more efficient and a cost-effective strategy. Adolescents should be more aware of HPV. They must be encouraged to postpone the initiation of their sexual activity, in order to allow the cervix to mature, before exposure to HPV [6]. Sexual abstinence and mutually monogamous sexual relationships although recommended are not realistic or feasible [14]. Efforts should be focused on "selective sex" rather than on "safe sex" behaviors such as delaying first coitus, limiting the number of sexual partners and choosing partners who have been selective [6]. It has already been stated that condom use is not very efficient in preventing HPV transmission. However, it is highly effective in reducing other sexually transmitted diseases, like Chlamydia trachomatis or HSV which are important risk factors for HPV and cervical cancer. Changes in lifestyle should also be made, including abstinence from alcohol and tobacco use, and appropriate amelioration of the diet which will have a positive effect on the condition of their immune system [6].

It is accepted that the most beneficial impact on human health was obtained by vaccinations during childhood. Large-scale vaccination programs have controlled diseases with great morbidity and mortality [26]. During the last 20 years many researches have focused on the development of anti-HPV vaccines. Till now much progress has been made. This effort is hindered by the main strains of the virus and therefore little knowledge is known about which strains are oncogenic and which may stimulate the immune system without transforming the cells [6]. There are two categories of vaccines in development. Prophylactic vaccines, whose targets are L1 and L2 proteins of the viral capsid, are designed to prevent primary HPV infection by including virus-neutralizing antibodies. The ideal age of vaccination has proven to be nine to 13 years old, in order to protect the most vulnerable young adolescents and to confer immunity before initiation of sexual activity [27, 28]. Vaccination programs should include both girls and boys because males are an important vector in the transmission of the virus, and they can develop both genital warts and anogenital cancer [27]. An ideal HPV vaccine should be characterized by safety, efficacy and cost effectiveness. In addition, vaccines should be feasible for low resource settings; that is the reason why they would be inexpensive, they would not require refrigeration and they would be effective after one single dose providing long-lasting immunity [26].

The success of HPV vaccination programs depends on individuals' willingness to accept it, on parents' willingness to have their children vaccinated and on healthcare providers' willingness to recommend HPV vaccinations [27]. HPV educational efforts need to be made in order to increase vaccine acceptance [29]. There are a lot of parents afraid to have their children vaccinated because they think it would lead to risky sexual behavior [30]. However, education does not imply that HPV vaccine will be widely accepted because HPV is a sexually transmitted disease where there is still a stigma [27]. Despite all these factors it is widely accepted that large-scale HPV vaccination programs will reduce HPV infection, genital warts and cervical cancer both in developed and developing countries where screening programs (Papanicolaou test) have principally failed.

The second category includes therapeutic vaccines, designed to prevent progression of HPV infection to LG or HGSIL, to regress CIN or condylomata or to extirpate remnant cervical cancer. The aim of therapeutic vaccines is the elimination of E6 and E7 proteins, which are associated with cancer by eliciting a cell-mediated cytotoxic t-cell response.

Summary

Adolescents who are sexually active are at high risk of acquiring HPV and other sexually transmitted diseases, the majority of which are self-sustained by the immune system. However, HPV may lead to genital warts, cervical dysplasia and cervical cancer. Cervical cancer is the result of a chronic and persistent infection with high-risk HPV types. Other risk factors such as risky sexual behavior (early age of first intercourse, great number of sexual partners), smoking, immunosuppression and infections with other sexually transmitted diseases play an impor-

tant role in the progression of cervical cancer. Sexually active adolescent females should be encouraged to obtain gynecologic screening for HPV and cervical cancer. In addition all adolescents should be well informed about HPV and the risks associated with this infection. LGSIL in adolescents is better to be observed than treated by using repeat cytology or HPV DNA testing because it is usually transient in this population. All efforts are now focused on developing vaccines that are expected to reduce morbidity and mortality associated with HPV infection if administered before initiation of sexual activity.

References

[1] Kahn J.A., Rosenthal S.L., Succop P.A., Ho G.Y., Burk R.D.: "The interval between menarche and age of first sexual intercourse as a risk factor for subsequent HPV infection in adolescent and young adult women". *J. Pediatr.,* 2002, *141*, 718.

[2] Kahn J.A.: "An update on HPV infection and Papanicolaou smears in adolescents". *Curr. Opin. Pediatr.,* 2001, *13,* 303.

[3] Moscicki A.B., Ellenberg J.H., Farhat S., Xu J.: "Persistence of human papillomavirus infection in HIV-infected and -uninfected adolescent girls: risk factors and differences, by phylogenetic type". *J. Infect Dis.,* 2004, *190,* 37.

[4] Deligdisch L., de Resende Miranda C.R., Wu H.S., Gil J.: "Human papillomavirus-related cervical lesions in adolescents: a histologic and morphometric study". *Gynecol. Oncol.,* 2003, *89,* 52.

[5] Centers for Disease Control and Prevention (CDCP): "Tracking the hidden epidemic: Trends in sexually transmitted diseases in the U.S. - 2000". Atlanta: Department of Health and Human Services, Division of Sexually Transmitted Disease Prevention, 2000.

[6] Cothran M.M., White J.P.: "Adolescent behavior and sexually transmitted diseases: the dilemma of human papillomavirus". *Health Care Women Int.,* 2002, *23,* 306.

[7] Moscicki A.B., Hills N., Shiboski S., Powell K., Jay N., Hanson E. *et al.*: "Risks for incident human papillomavirus infection and low-grade squamous intraepithelial lesion development in young females". *JAMA,* 2001, *285,* 2995.

[8] Moscicki A.B.: "Impact of HPV infection in adolescent populations". *J. Adolesc. Health.*, 2005, *37* (suppl. 6), S3.

[9] Frega A., Stentella P., De Ioris A., Piazze J.J., Fambrini M., Marchionni M. *et al.*: "Young women, cervical intraepithelial neoplasia and human papillomavirus: risk factors for persistence and recurrence". *Cancer Lett.,* 2003, *196,* 127.

[10] Smith E.M., Ritchie J.M., Summersgill K.F., Klussmann J.P., Lee J.H., Wang D. *et al.*: "Age, sexual behavior and human papillomavirus infection in oral cavity and oropharyngeal cancers". *Int. J. Cancer,* 2004, *108*, 766.

[11] Simsir A., Brooks S., Cochran L., Bourquin P., Ioffe O.B.: "Cervicovaginal smear abnormalities in sexually active adolescents. Implications for management". *Acta Cytol.,* 2002, *46*, 271.

[12] Vaccarella S., Herrero R., Snijders P.J., Dai M., Thomas J.O., Hieu N.T. *et al.*: "The IARC HPV Prevalence Surveys (IHPS) Study Group. Smoking and human papillomavirus infection: pooled analysis of the International Agency for Research on Cancer HPV Prevalence Surveys". *Int. J. Epidemiol.,* 2008, *37*, 536.

[13] Vetrano G., Lombardi G., Di Leone G., Parisi A., Scardamaglia P., Pate G. *et al.*: "Cervical intraepithelial neoplasia: risk factors for persistence and recurrence in adolescents". *Eur. J. Gynaecol. Oncol.,* 2007, *28*, 189.

[14] Lazcano-Ponce E., Rivera L., Arillo-Santillan E., Salmerón J., Hernández-Avila M., Muñoz N.: "Acceptability of a human papillomavirus (HPV) trial vaccine among mothers of adolescents in Cuernavaca, Mexico". *Arch. Med. Res.,* 2001, *32,* 243.

[15] Finan R.R., Musharrafieh U., Almawi W.Y.: "Detection of Chlamydia trachomatis and herpes simplex virus type 1 or 2 in cervical samples in human papilloma virus (HPV)-positive and HPV-negative women". *Clin. Microbiol. Infect.,* 2006, *12,* 927.

[16] Guido R.: "Guidelines for screening and treatment of cervical disease in the adolescent". *J. Pediatr. Adolesc. Gynecol.,* 2004, *17,* 303.

[17] Szarewski A., Sasieni P.: "Cervical screening in adolescents-at least do no harm". *Lancet,* 2004, *364*, 1642.

[18] Gerhardt C.A., Pong K., Kollar L.M., Hillard P.J., Rosenthal S.L.: "Adolescents' knowledge of human papillomavirus and cervical dysplasia". *J. Pediatr. Adolesc. Gynecol.,* 2000, *13,* 15.

[19] Moscicki A.B., Ellenberg J.H., Crowley-Nowick P., Darragh T.M., Xu J., Fahrat S.: "Risk of high-grade squamous intraepithelial lesion in HIV-infected adolescents". *J. Infect. Dis.,* 2004, *190,* 1413.

[20] Moscicki A.B.: "Cervical cytology testing in teens". *Curr. Opin. Obstet. Gynecol.,* 2005, *17,* 471.

[21] Sjøborg K.D., Vistad I., Myhr S.S., Svenningsen R., Herzog C., Kloster-Jensen A. *et al.*: "Pregnancy outcome after cervical cone excision: a case-control study". *Acta Obstet. Gynecol. Scand.,* 2007, *86*, 423.

[22] Kahn J.A., Hillard P.A.: "Human papillomavirus and cervical cytology in adolescents". *Adolesc. Med Clin.,* 2004, *15,* 301.

[23] Gray S.H., Walzer T.B.: "New strategies for cervical cancer screening in adolescents". *Curr. Opin. Pediatr.,* 2004, *16,* 344.

[24] Gingrich P.M.: "Management and follow-up of abnormal Papanicolaou tests". *J. Am. Med. Womens Assoc.,* 2004, *59,* 54.

[25] Moscicki A.B.: "Cervical cytology screening in teens". *Curr. Womens Health Rep.*, 2003, *3*, 433.

[26] Kahn J.A.: "Vaccination as a prevention strategy for human papillomavirus-related diseases". *J. Adolesc. Health.,* 2005, *37* (suppl. 6), S10.

[27] Zimet G.D.: "Improving adolescent health: focus on HPV vaccine acceptance". J. Adolesc. Health., 2005, *37* (suppl. 6), S17.

[28] Kahn J.A., Zimet G.D., Bernstein D.I., Riedesel J.M., Lan D., Huang B. *et al.*: "Pediatricians' intention to administer human papillomavirus vaccine: the role of practice characteristics, knowledge, and attitudes". *J. Adolesc. Health.,* 2005, *37*, 502.

[29] Olshen E., Woods E.R., Austin S.B., Luskin M., Bauchner H.: "Parental acceptance of the human papillomavirus vaccine". *J. Adolesc. Health.*, 2005, *37,* 248.

[30] Davis K., Dickman E.D., Ferris D., Dias J.K.: "Human papillomavirus vaccine acceptability among parents of 10- to 15-year-old adolescents". *J. Low Genit. Tract. Dis.,* 2004, *8,* 188.

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