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Review

Human papillomavirus infection in couples with female low-grade intraepithelial cervical lesion

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ABSTRACT

Low-grade squamous intraepithelial lesions (LSIL) are frequently found during cervical cancer screening. Usually they are associated with a human papillomavirus (HPV) infection. Does the high-transmission rate of HPV infection to the male partner represent a clinical risk for him? Are preventive measures to be taken to prevent the occurrence of male diseases?

More than 80% of all LSIL are associated with HPV infections. The prevalence of HPV infection in males can range up to 40%, with 60% of the male partners of LSIL female patients presenting with penile flat lesions. The spontaneous cure rate for male infections is very high (90% at 5 years) but negative consequences in females (cervical high-grade lesion and cervical cancer) are frequent. Their male counterparts are far rarer but in some patients can require deleterious treatment. Transmission prevention by the use of condoms and circumcision is discussed. The effectiveness of HPV vaccination in this situation has not been validated.

Contents

1. Introduction

Low-grade squamous intraepithelial lesions (LSIL) are frequently found during screening for cervical cancer. Analyzing 9297 cervical samples from Flanders, Arbyn et al. [1] describe a 2.6% frequency of LSIL in the studied population. The mean age of the patients studied was 42 years, with only 10% of patients younger than 25 years of age. In our department, in a series of 27,500 smears, we observed [2] an average LSIL frequency of 1.8% (2.95% before 30 years of age, 1.3% after 30). These lesions are most often associated with human papillomavirus (HPV) infection. Knowing the high-transmission rate of these viral infections during sexual contact, it is therefore logical to consider the potential risks this represents for the male partner. Does the acquisition of HPV during sexual intercourse with an LSIL patient represent a danger for his health? Does he need to protect himself through exclusive condom use? Does condom use by the male alter the evolution of the lesions in the female?

2. LSIL: the risk for the woman

LSIL is a cytologic definition, meaning that a lesion must be histologically defined before a therapeutic decision is taken. The biopsy is done, according to the protocol used, either immediately after a colposcopy is performed, or after a second cytology displaying the same abnormality 6 months later.

The prevalence of LSIL in a low-risk population was estimated to be 2.6%. The cervix of 70% of these patients displays a low-grade dysplasia (CIN 1) and of 15–30% a severe dysplasia (CIN 2 & 3), with no lesions found in the remaining patients [3,4].

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Papillomavirus infection was found in 85% of samples using Multiplex real-time PCR in the LSILs in a large population in Belgium [1] (10,000 liquid cervical cell samples collected in 2006 representing ± 200 LSILs), which is a result similar to the one (83%) published earlier by the ALTS group [5] in a larger number of patients. This frequency rose to 98% in the French EDITH III study [6] of 397 smears with LSIL. In our study [2], we found an 88% frequency of HPV positivity.

The type of papillomavirus found differs from one country to another. In the French study, HPV 66 (low-risk) was the one most often found (24.9%), followed by HPV 16 (21%), HPV 53 (18%), 51 (17%) and 52 (14%). This distribution is different from the one seen in the very geographically close country of Belgium, where HPV 16 was the most often found (23.5%), followed by HPV 31 (22.2%), HPV 6 (16%), 53 and 39 (14.8%), 51 (14.4%), and 66 (14%). The two series differ in their age distribution, with a mean age of 42 for the Belgian one and 31 years for the French one, which might explain the difference observed.

Clifford et al. [7] pooled data from cytological and biological samples of LSIL. They observed a similar hierarchy with HPV 16 as the most common followed by HPV 31, 51 and 53. Other geographic variations have been evidenced, indicating a relative reduction in the incidence of HPV 16 in Africa and an increased risk for the association of LSIL and HPV 18 in the United States.

Analysis of a large population-based cohort [8] indicated a 6-month clearance rate of HPV infections in 29% of cases of borderline/mild type dyskaryosis (BMD). This clearance rate increased to 41% after an 18-month period. A significantly reduced HPV clearance at 18 months was observed in cases of HPV 16 infection (19% clearance).

Multiple infections are frequent in low-grade cytology and are observed in up to 50% of cases [5]. In a series of 187 patients, Moscicki et al. [9] describe a 61% regression rate at 12 months in a young (13–22 years) population. The cure increased to 91% at 36 months. In this series, patients suffering from multiple HPV infections did not display a lower regression rate than those presenting a single type infection. On the contrary [10], an older age (Hazard ratio = 0.61 for 50–59 year of age and 0.30 over 60) and a high-viral load ($>10^3$ copies/100 ng) negatively influence the clearance rate of HPV infections.

Maintenance and progression of LSIL to high-grade lesions are frequent. A prospective study [11] in which 125 women had an LSIL displayed a 24% progression to cervical high-grade lesion after 12 months. The progression rate is influenced by several factors but depends largely on the HPV type [12]. Patients with a persistent HPV 16 infection [8] have a higher risk of progression to CIN 3+ (38 vs. 26% for the total HPV-persistent BMD population). Multiple HPV-infected patients [3] were found to present a 15–27% risk of developing CIN2+ lesion. True HPV-negative patients are quite rare [13] as repeat testing decreased their frequency to 3–11% of all LSILs. The risk of these patients presenting with a high-grade histological lesion (2–4%) was lower than of the HPV-positive population (13–19%) [9].

3. HPV infection in men

Reviewing 40 publications on HPV infection in men, Dunne et al. [14] reported a prevalence of HPV infection in men ranging from 1.3 to 73%. The majority of the studies report a prevalence of over 20% depending on the population, the sampling sites and the processing methods.

HPV infection can present as an invisible ano-genital lesion or any stage of lesion up to squamous cell carcinoma. Genital warts are very common, with a prevalence estimated to be 1% of the sexually active male population between 15 and 49 years; they are most often associated with HPV 6 and 11 infections (associated with 70–100% of exophytic genital warts). The peak for genital warts in both sexes occurs between 20 and 24 year of age.

The "flat lesions" that are revealed by acetic acid application in up to 60% partners of the patients presenting with HPV-associated CIN are more likely to be caused by high-risk HPV [15]. They are located mainly at the distal part of the penis and inner surface of the prepuce where the infection is presumed to be transmitted. Follow-up of these lesions showed shortened mean regression time (7.4 months) when condoms were used regularly when compared with a group of non-users (13.9 months) [15].

HPV 16 is the most often encountered (prevalence 8.6% in a male population [16] between 18 and 44 year of age) but multiple infections are very frequent. The risk of acquiring an oncogenic type during a 12-month period appears to be greater than the risk for a non-oncogenic type (19 vs. 16% over a 12-month period). Clearance of the infection in males is rapid, as 75% of all infections disappear within a 12-month period. The median clearance time was 5.9 months, without any difference between HPV 6/11 and high-risk HPV 16 and 18 [16]. A similar prevalence is observed in men and women with the same incidence of HPV infection [17,26]. Contrary to what has been described in women, no association between age and duration of infection has been evidenced in males.

The risk factors for HPV infections in men are similar to their female counterparts: age at first sexual intercourse, number of partners, high frequency of intercourse and immuno-deficiency syndrome. HIV-positive men (and especially men who have sex with men) have a high risk (59%) of developing Anal Intraepithelial Neoplasia [18]. A small proportion of these had Penile Intraepithelial Neoplasia (PIN) (4%) but it appears that the higher the grade of AIN, the greater the risk for PIN. A high-grade AIN was primarily associated (8.5%) with PIN2 and 3.

The preferential localization of the lesions in men is still under debate [19]. The most common site of warty lesions is the shaft; in uncircumcised men, however, a more distal infection is more likely. The penile shaft presents the higher viral load [20] of all the male genitalia and seems to be the preferred site for replication. It is also the place where most multiple HPV infections are seen.

The role and benefit of male circumcision has also been discussed as it has been claimed this procedure could reduce [21] the spread of HPV infection in developing countries. It appears that the location of HPV lesions varies in the male genitals depending on whether circumcision has been performed or not. Indeed, HPV is found preferably on the shaft of circumcised men and on the glans of uncircumcised ones. If only the glans (and not multiple sites including the shaft) is sampled, the risk of infection is underestimated by 35% in circumcised men, considerably reducing the benefit of this surgical procedure in the prevention of infection [22].

Similarly to what is observed in vulvar cancer, HPV positivity is more often seen in non-invasive ano-genital diseases than in invasive ones: carcinoma in situ and PIN are frequently associated with an HPV 16 infection. The same type is found in anal cancer, of which 58–100% are associated with oncogenic HPV. Invasive penile cancer is a rare disease in developed countries (incidence ranges between 0.3 and 1 per 100,000 men) for a total of 4000 cases per year in Europe [23]. In developing countries (e.g., Brazil, Columbia and Uganda), however, incidences up to 4/100,000 are observed. The vast majority of invasive squamous cell carcinoma is linked to HPV 16 or 18 even if DNA positivity is more often seen in non-invasive than in invasive lesions [24]. However, some variants like verrucous carcinoma could be linked with HPV 6 and 11 [25]. This relatively small incidence in comparison to the cervical carcinoma probably derives from the absence of a transformation zone on the penis (but which is present in the anal canal) that makes the attachment of HPV difficult [18].