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Anal study in immunocompetent women with human papillomavirus related lower genital tract pathology

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ABSTRACT

Objetive: To estimate the prevalence of anal dysplasia in immunocompetent women with cervical intraepithelial dysplasia.
Study design: We did a prospective cohort study, in which we enrolled 166 women with gynecological pathology related to human papilloma virus (HPV) infection. All patients underwent an anal cytology and HPV detection. Statistical analysis with a 95% confidence interval was used for prevalence calculations. A X2 test and Fisher's exact one were used to determine differences between groups of qualitative variables. Differences between normally distributed and non-normally distributed groups in quantitative variables were accounted for using Student's *t*-test or Mann-Whitney's *U* test, respectively.
Results: Out of the 166 patients studied, high risk HPV in the anal canal was detected in 107 (64.46%) cases. The most prevalent genotype observed was non 16/18 high risk HPV, present in 54 (50.47%) patients. There was no a significant association with smoking, use of condom, anal intercourse, or anal benign pathology. However, a significant correlation between the presence of high risk HPV in the anal canal and the antecedent of condylomas was observed (p = 0.047) (CI95%: 1.00%–12.58%). Women with cervical intraepithelial neoplasia (CIN) grade 1 had a significantly increased presence of high risk HPV in the anal canal (p = 0.044). Out of the 166 women, 6 (3.61%) had abnormal anal cytology results, and were referred to high-resolution anoscopy. Anal biopsy was performed in these six cases. In 2 patients the biopsy reported low-grade Anal Intraepithelial Neoplasia: 1.20% (0.15%–4.28%).
Conclusions: Women with cervical intraepithelial dysplasia have 1.20% prevalence of anal intraepithelial neoplasia, so that it does not seem necessary to screen this population.

Introduction

The Human Papillomavirus infection plays an important role in the etiopathogenesis of anal cancer. Most of these, 90%–96%, are HPV dependent [1–3]. HPV 16 is the most prevalent, present in 65.6% of the cases according to Darragh [4] and 81% according to Ouhoummane [3].

Anal cancer is relative rare in general population [5], but the incidence and mortality have experimented a worldwide progressive increment since 1975 [6] rising up to 1–2 per 100.000 [7]. In women, the prevalence is 2.06 per 100.000 [8]. According to the American Society of Cancer in 2014, some 7210 new cases of anal cancer will occur in USA, including 4550 (63%) women [9]. The risk factors for development of anal cancer include [5,10]: HIV disease, men who have sex with men, receptive anal intercourse [11,12], number of sexual partners, history of genital warts, smoking, prolonged immunosuppressive therapy [13,14], anal fissures and fistulas [15] and in women, the antecedent of lower genital tract squamous intraepithelial neoplasia [16–20].

Regarding immunocompetent women with cervical dysplasia, there are very few publications available: Park [21], Santoso [22], Jacyntho [23], Lamme [6], and Scholefield [24], which published prevalence rates of 9%, 12.2%, 17.4%, 17.6% and 19% respectively.

Patients with high-grade cervical dysplasia and cervical carcinoma are more likely to develop anal cancer and anal intraepithelial neoplasia (AIN) [19,20,25]. For some authors, CIN 3 involves an incidence of anal cancer 4 or 5 times higher than in the general population [26,27].

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There are no universally standardized guidelines for screening program for precancerous anal lesions [28]. Palefsky's group [29] was the first to introduce anal cytology in this screening. They proposed an algorithm of action based on screening for cervical cancer [27,29,30]. Currently, the anal Pap test is the primary screening for anal cancer.

High Resolution Anoscopy (HRA) is the gold standard for diagnosis of high-grade AIN after abnormal cytology [31,32].

The majority of studies have focused on homosexual men and in HIV disease [23] and not in immunocompetent women with cervical dysplasia.

The aim of the present study is to determine the prevalence of anal dysplasia in immunocompetent women being studied and treated for cervical dysplasia in our department.

Materials and methods

Study design

This was a prospective cohort study. Participants were recruited from July 2013 to March 2015, out of women who were treated at the Hospital's Gynecological Lower Genital Tract and Colposcopy Unit. A total of 166 immunocompetent women with gynecological pathology related to HPV infection were enrolled in this anal lesions study. Women were eligible for inclusion if they had either persistent viral infection, or ASCUS (atypical squamous cells of undetermined significance) cytology, or ASC-H (atypical squamous cells, cannot exclude high grade squamous intraepithelial lesion) or LSIL (low-grade intraepithelial lesion) or HSIL (high-grade intraepithelial lesion), or histologically confirmed CIN grade 1, 2 or 3.

This study excluded pregnant women, as well as HIV-positive, non-HIV immunocompromised, and those previously treated for CIN.

At the first visit, all patients signed an informed consent form and were interviewed in person about their medical history and their sexual habits. Participants underwent colposcopy examination and screening of anal dysplasia, which included HPV typing and anal liquid based cytology. The sample taken for anal cytology and HPV tests was performed with cytobrush and preserved in liquid medium, using the ThinPrep preparation (Hologic, Inc., Marlborough, MA). The anal cytology results were classified according to the Bethesda System 2001 as normal, ASCUS, LSIL, ASC—H, HSIL or cervical carcinoma.

Sample collected material was tested for HPV with HC2 HPV DNA assay (Digene®) and Cobas® HPV test. Patients with anal positive cytology (ASCUS or more) were sent to the specific Colorectal Surgery Unit, for performing HRA.

Sample size

The sample size was calculated to achieve the main objective of the study, knowledge of the prevalence of anal dysplasia in women with HPV infection related lesions of the lower genital tract. According to literature, the prevalence range oscillates between 9% and 19%, so we assumed the prevalence to be around 10%. This prevalence was estimated with a 95% confidence interval, with a $P < 0.05$ significance level and a probability of obtaining favorable results of 80%. Using Ene 2.0 (GlaxoSmithKline, Barcelona, Spain) the required sample size to reach significance was at least 150.

Data analysis

Statistical analysis with a 95% confidence interval was used for prevalence calculations. A X2 test and Fisher's exact one were used to determine differences between groups of qualitative variables. Differences between normally distributed and non-normally distributed groups in quantitative variables were accounted for using Student's *t*-test or Mann-Whitney's *U* test, respectively.

A p-value < 0.05 was considered statistically significant with the use of a two-sided test. The statistical analysis was carried out using SPSS 20.0 (Statistical Package for the Social Sciences, SPSS Inc, Chicago, IL, USA).

The study protocol was approved by the Research Ethics Committee of Hospital General Universitario of Alicante.

Results

The final study cohort included a total of 166 immunocompetent women with an average age at recruitment of 38 years (range 22–71). All of them underwent an anal citology and an HPV test. Table 1 shows the demographic characteristics of the study population.

Among the 166 women studied, HR HPV in the anal canal was detected in 107 (64.46%) cases. Of these, the most prevalent genotype observed was non 16/18 HR HPV, present in 54 (50.47%) cases, followed by 16/18 HR HPV in 51(30.72%) cases, unspecified HR HPV in 36 (21.69%) cases and not determined in 16 (9.64%) cases.

Table 2 shows the risk factors for anal HPV infection.

Anal cytologic abnormalities were detected only in 6/166 samples (3.61%). Four patients had ASCUS and there were 2 diagnoses of LSIL. In five of the six cases, the HR HPV was detected in the anal canal (in the other one we identified HPV genotype 6) (Table 3). The age of the 6 patients was between 24 and 49 years. None of them smoked or had a history of genital herpes. One had an antecedent of anal fissure, and two women had a history of perianal warts. The age of first intercourse was between 17 and 22 years. Five patients practiced unprotected vaginal coitus. Four of them were non-oral contraceptive users. Only one had no regular sexual partner, lasting their relationships between 1 and 17 years. Regarding the practice of anal intercourse, three claimed not to have, and the other three had only sporadic anal intercourse (between 1 and 2 times a year).

Table 1
Demographic characteristics of the study population.

Characteristics	N [Range]	% (95% CI)
Mean Age [Range]	38 [22–71]	
Age at first intercourse	18 [13–26]	
Current Smokers	70	42.17% (34.56–50.07)
Condom users		
Never	80	48.19% (40.38–56.07)
User	57	34.34% (27.15–42.09)
Ocasionally	29	17.47% (12.02–24.12)
Oral Contraceptives	24	14.46% (9.49–20.74)
Number of sexual partners		
1	8	4.82% (2.10–9.27)
2–5	117	70.48% (62.92–100)
>5–10	29	17.47% (12.02–24.12)
>10–20	12	7.23% (3.79–12.29)
Regular sexual partner	96	57.83% (49.93–65.44)
Receptive anal Intercourse. Yearly frecuency		
Never	115	69.28% (61.66–76.19)
1–10	34	20.48% (14.62–27.43)
>10–365	17	10.24% (6.08–15.89)
Without Anal Benign Pathology	105	63.25% (54.43–70.59)
History of Herpes genitalis	9	5.42% (2.51–10.04)