THE JOURNAL OF
Obstetrics and Gynaecology Research
The official Journal of Asia and Oceania Federation of Obstetrics and Gynaecology
Japan Society of Obstetrics and Gynecology
doi:10.1111/jog.13225 J. Obstet. Gynaecol. Res. Vol. 43, No. 2: 352–357, February 2017

Screening for cervical carcinoma in HIV-infected women: Analysis of main risk factors for cervical cytologic abnormalities

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Abstract

Aim: The aim of this study was to identify potential predictive factors for cervical disease in women with HIV and to evaluate adherence during follow-up to cervical cancer screening.

Methods: In order to identify the independent role of factors associated with the presence of a cervical abnormality, all of the variables showing in univariate analyses a potential association with the outcome variable (presence of cervical abnormalities) were entered into a multivariate logistic regression model, along with age at first visit to our center, and age at diagnosis.

Results: A total of 540 HIV-positive women who received screening for cervical cancer during the first year after their first visit to our center were included in the analysis; 423 (78.3%) had normal cytology and 117 (21.7%) had cytological abnormalities, classified as follows: 21 atypical squamous cells of undetermined significance (17.9%); 51 low-grade squamous intraepithelial lesions (43.6%); 41 high-grade squamous intraepithelial lesions (35.0%); and four cervical cancers (3.4%). In our study, women with more than two previous pregnancies were significantly associated with a lower risk of cervical cytological abnormalities compared to the other women. Women with CD4+ levels of 200–499/mm^3 had a higher risk of developing cervical cytological abnormalities compared to those with a CD4+ level $>$ 500/ mm^3.

Conclusion: In summary, management of HIV-positive women must be modeled on HIV-clinical status, CD4+ cell count, drug regimen, and adherence to follow-up, relying on the cooperation of highly qualified professionals. In HIV-positive women, an adequate screening and follow-up allows for a reduced occurrence of advanced cervical disease and prevents recourse to invalidating surgical interventions.

Key words: cervical cancer, colposcopy, highly active antiretroviral therapy, HIV, screening.

Introduction

Cervical cancer represents one of the most serious gynecologic manifestations in women with HIV infection.[1,2] Since 1993, the revised Centers for Disease Control and Prevention AIDS case definition has included the development of cervical cancer in an HIV-infected woman as a sufficient criterion for a clinical diagnosis of AIDS, even in the absence of other opportunistic diseases.[3] In HIV-infected women, there is an increased risk of human papillomavirus (HPV) infection and squamous intraepithelial lesions (SIL), with an annual incidence fivefold higher than that of the general population (8.3/100 women years vs 1.8/100 women years), and a threefold increase in the risk of developing invasive cervical cancer.[4,5] Multiple prospective studies have

Received: June 8 2016.
Accepted: September 23 2016.
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demonstrated that women with HIV infection are much more likely than HIV-negative women to have persistent HPV, often with oncogenic subtypes.[6–8] Thus, compared with HIV-negative women, HIV-positive women are more likely to progress to cervical cancer, have a worse prognosis, and are at higher risk of recurrence or persistence.[9,10] Prevention of cervical cancer relies on the detection and treatment of SIL, a premalignant disease stage.

The purpose of this study was to identify potential predictive factors for cervical disease in women with HIV and to evaluate adherence during follow-up to cervical cancer screening guidelines in this particular group of women.

Methods

This was a retrospective observational study. Screening data from Papanicolaou (Pap) smears and colposcopic examinations were collected in HIV-positive women who attended the Center for STD and HIV/AIDS at the Department of Obstetrics and Gynecology, University of Naples Federico II between January 2005 and January 2010.

In addition to the standardized questionnaire, which is given on admission to all of the women attending our center and collects information on age, history of STD, number of pregnancies, history of Pap smears, number of sexual partners, country of origin, and ethnicity, women with HIV were also evaluated for HIV route of transmission, time from HIV diagnosis, possible illicit drug abuse, HIV-related clinical events, and CD4+ cell count (both determined in the 6 months preceding the Pap smear and the colposcopic examination).

For each patient, we collected data from the Pap smear and colposcopic examination, and recommended a follow-up cytology evaluation after 6 months for women with CD4+ cell count $< 200/mm^3$ and after 1 year for women with CD4+ cell count $> 500/mm^3$.[11] Cytological and histological samples were reviewed by the pathologist of the Department of Biomorphological and Functional Science, University Federico II of Naples. Abnormalities on the Pap smear and biopsy results were rated according to the Bethesda System classification.[12] Colposcopic examinations were performed by a colposcopist, and the findings were rated according to the International Federation of Cervical Pathology and Colposcopy format (2007).[13] To assess the adherence (i.e. at least annually) of women with HIV to the screening program, the 5- and 10-year outcomes according to the Italian Society of Colposcopy and Cervical Pathology guidelines (2006) were used.[14]

Statistical analysis was performed using SPSS ver. 19.0 (IBM Inc.) by a professional statistician (D.B.). Because there were substantial missing data for the variables describing the partner's HIV status and transmission route (27.2%), a multiple imputation (MI) procedure was used. Ten different complete datasets were generated using the MI by chained equation algorithm. Due to the categorical nature of the variable with missing information, a polytomous regression model was used as the imputation model; all the study variables (Table 1)[15] were entered as covariates in the MI analysis.

Data were summarized as means (±SD) for continuous variables and as frequencies (%) for categorical variables. Univariate differences between the two groups (women with or without any of the following cervical abnormalities: atypical squamous cells of undetermined significance [ASCUS], low-grade squamous intraepithelial lesions [LSIL], high-grade squamous intraepithelial lesions [HSIL], and cervical cancer [CC] on Pap smear) were assessed with the Student's *t*-test for independent samples in case of continuous variables and with the χ^2-test (or Fisher's exact test if appropriate) in case of categorical variables.

To identify the independent role of factors associated with the presence of a cervical abnormality, all the variables showing in univariate analyses a potential association ($P < 0.25$) with the outcome variable (presence of cervical abnormalities) were entered into a multivariate logistic regression model, along with age at first visit to our center, and age at diagnosis (Table 2).

Multiple logistic regression was based on MI of missing data. A sensitivity analysis based on available data only gave highly consistent results (data not shown). Associations between potentially predictive factors and the outcome variable were reported as adjusted odds ratios (AOR) with 95% confidence intervals (CI).

Two-sided *P*-values < 0.05 were considered statistically significant. All statistical analyses were conducted using the statistical platform R ver. 2.12 (R Development Core Team 2010).

Results

A total of 540 HIV women received screening for cervical cancer during the first year after their first visit to our center and were therefore included in the analysis; 423 (78.3%) had normal cytology and 117 (21.7%) had cytological abnormalities, classified as follows: 21 ASCUS

Table 1 Demographic characteristics and risk factors for abnormal cervical cytology at enrollment

	Women with normal cervical cytology (n = 423)	Women with abnormal cervical cytology (n = 117)†	All (n = 540)	P
Age at first visit to our center (years)	33.3 ± 7.2	33.8 ± 8.0	33.4 ± 7.4	0.52
Age at HIV diagnosis (years)	29.5 ± 7.5	30.4 ± 8.1	29.8 ± 7.6	0.28
Smoking	120 (28.4%)	35 (29.9%)	155 (28.7%)	0.84
Geographic area of origin				
Italy	299 (70.7%)	75 (64.1%)	374 (69.3%)	0.52
Eastern Europe	19 (4.5%)	7 (6.0%)	26(4.8%)	
Africa	86 (20.3%)	29 (24.8%)	115 (21.3%)	
Other (Western Europe, America, Asia)	19 (4.5%)	6(5.1%)	25 (4.7%)	
Route of transmission of HIV				
Heterosexual intercourse	315 (74.5%)	100 (85.5%)	415 (76.8%)	0.03
Drug abuse	94 (22.2%)	16 (13.7%)	110 (20.4%)	
Other (blood transfusion, unknown, vertical transmission, occupational transmission)	14 (3.3%)	1 (0.8%)	15 (2.8%)	
Previous pregnancies				
0	110 (26.0%)	38 (32.5%)	148 (27.4%)	0.13
1–2	170 (40.2%)	46 (39.3%)	216 (40.0%)	
>2	143 (33.8%)	33 (28.2%)	176 (32.6%)	
CD4+ cell count/mm^3				
≥500	110 (26.0%	13 (11.1%)	123 (22.8%)	<0.001
200–499	243 (57.4%))	59 (50.4%)	302 (55.9%)	
<200	70 (16.6%)	45 (38.5%)	115 (21.3%)	
Antiretroviral therapy				
None	224 (53.0%)	55 (47.0%)	279 (51.7%)	0.27
Mono- or dual NRTI therapy	112 (26.4%)	40 (34.2%)	152 (28.1%)	
HAART	87 (20.6%)	22(18.8%)	109(20.2%)	
Partner's HIV status and transmission route‡				
Heterosexual or transfused HIV-positive	180 (42.6%)	36 (30.8%)	216 (40.0%)	0.14§
Drug abuser HIV-positive	141 (33.3%)	48 (41.0%)	189 (35.0%)	
HIV-negative	102 (24.1%)	33 (28.2%)	135 (25.0%)	
Number of lifetime sexual partners				
<5	272 (64.3%)	53 (45.3%)	325 (60.2%)	$P < 0.001$
≥5	151 (35.7%)	64 (54.7%)	215 (39.8%)	

†Of these 117 women, 21 had atypical squamous cells of undetermined significance, 51 had low-grade squamous intraepithelial lesions, 41 had high-grade squamous intraepithelial lesions, and four had cervical cancer. ‡Frequencies have been computed as unweighted average over the 10 complete datasets generated by multiple imputation. §P-value was obtained according to the procedure described in Li *et al.*[15] HAART, highly active antiretroviral therapy; NRTI, Nucleoside reverse transcriptase inhibitors.

(17.9%); 51 LSIL (43.6 %); 41 HSIL (35.0%); and four cervical cancers (3.4%). The main epidemiological and clinical features of the women with and without cytological abnormalities are summarized in Table 1. None of the women included in the study had been vaccinated against HPV.

In our study, women with more than two previous pregnancies were significantly associated with a lower risk of cervical cytological abnormalities (odds ratio [OR]: 0.50; 95% CI: 0.28–0.91; P = 0.022) compared to other women. Patients with CD4+ levels < 200/ mm^3 had a higher risk of developing cervical cytological abnormalities compared to those with a CD4+ level > 500/ mm^3 (OR: 5.22; 95%CI: 2.55–10.69; P < 0.001). Women with CD4+ levels of 200–499/mm^3 had a higher risk of developing cervical cytological abnormalities compared to those with a CD4+ level > 500/mm^3 (OR: 2.05; 95%CI: 1.05–3.98; P = 0.0035). Having five or more lifetime sexual partners was also associated with an increased risk compared to women with fewer than five lifetime sexual partners (OR: 3.47; 95%CI: 2.55–10.69; $P < 0.001$).

During a mean follow-up of 4.5 years (range, 1–10 years) among the 423 women with a normal or benign initial Pap smear, 183 (43.26%) did not receive cervical cancer screening, one woman died of a drug overdose, and 12 (2.83%) women were recently enrolled (between 2009 and 2010). Of the 183 women who did not repeat

Table 2 Risk factors for presence of cervical lesions†

	Adjusted odds ratio (95%CI)‡	*P*
Route of transmission of HIV, *n* (%)		
Heterosexual intercourse	1	—
Drug abuse	0.25 (0.12–1.12)	0.085
Other (blood transfusion, unknown, vertical transmission, occupational transmission)	0.28 (0.03–2.33)	0.240
Previous pregnancies (*n*)		
0	1	—
1–2	0.65 (0.38–1.12)	0.119
>2	0.50 (0.28–0.91)	0.022
CD4+ cell count/mm^3, *n* (%)		
≥500	1	—
200–499	2.05 (1.05–3.98)	0.035
<200	5.22 (2.55–10.69)	<0.001
Partner's HIV status and transmission route†		
Drug abuser HIV-positive	1	—
Heterosexual or Transfused HIV-positive	1.37 (0.74–2.53)	0.317
HIV-negative	1.55 (0.78–3.09)	0.213
Number of lifetime sexual partners		
<5	1	—
≥5	3.47 (2.55–10.69)	<0.001

†Cervical lesions included: atypical squamous cells of undetermined significance, low-grade squamous intraepithelial lesions, high-grade squamous intraepithelial lesions, and cervical cancer.
‡In addition to the variables reported above, odds ratios are adjusted for age at first visit to our center and age at diagnosis.

Pap smears after the first year, 68 (37.2%) were immigrants. Among the 423 patients with a normal benign initial Pap smear, 227 (53.66) received Pap smears within 5 years after the first visit and only 78 (18.43%) were screened for cervical cancer with a Pap test 10 years after their first visit. Among the 124 immigrant women who had a benign initial Pap smear, 68 (54.8%) did not repeat their Pap smears during follow-up.

After a mean follow-up of 4.5 years, four microinvasive cervical cancers and seven invasive cervical cancers occurred. Among these 11 patients with cervical cancer, six (54.5%) women had never undergone a Pap smear before their first visit to our center and five (45.5%) had had an interval of 4.2 (range, 2–5) years since their previous Pap smear. Two of these five women had had a normal cytology and three had had cytological abnormalities (two LSIL and one ASCUS). All of these 11 women were Italian; 10 (90.9%) of them had acquired HIV through heterosexual contacts and one probably through injection drug use (9.1%).

Discussion

One purpose of this study was to identify potential predictive factors for cervical disease in women with HIV. Highly active antiretroviral therapy (HAART) has dramatically changed the natural history of HIV, increasing CD4+ lymphocyte level, reducing the incidence of AIDS-related disease and prolonging survival.[16,17] The interactions among HIV, HPV, HAART, and the development of cervical neoplasia are not clearly understood, and the data on the impact of HAART on incidence and severity of cervical disease are often controversial. Data from countries with adequate resources do not point to a clear reduction in the burden and severity of cervical disease following introduction of HAART, in contrast to other AIDS-related malignancies (i.e. non-Hodgkin lymphoma).[18–21] Conversely, in a study on 168 patients treated with HAART, Heard observed a positive correlation between regression of cervical lesions and improvement of the immune system.[22] Minkoff found a reduced progression and increased regression of lesions.[23] In our study, the association between the variable antiretroviral therapy and the presence of cervical cytological abnormalities was not assessed, as we did not enroll women during the pre-HAART era.

Although the protective role of HAART against cervical disease is controversial, there is more agreement on the role of immunological status as a determinant factor in the development of cervical intraepithelial neoplasia among women with HIV.[23–25] Our study confirms the higher risk associated with more advanced immune deterioration, as shown by the higher risk to develop SIL among women with CD4+ levels < 200/mm^3 compared to women with CD4+ levels > 500/mm^3 (OR: 5.22; 95%CI: 2.55–10.69; $P < 0.001$).

In agreement with previous studies conducted internationally,[25–28] we also observed that a large number of lifetime sexual partners (>5) was associated with an increased risk of cervical abnormalities compared to women with a number of lifetime sexual partners < 5 (OR: 3.47; 95%CI: 2.55–10.69; $P < 0.001$).

In contrast to claims made by the scientific literature,[29–31] in our study, women with more than two previous pregnancies were significantly associated with a lower risk of cervical cytological abnormalities (OR: 0.50; 95% CI: 0.28–0.91; $P = 0.022$) compared to other women. A possible explanation for this result is that women with a large number of children tend to be sexually more stable than others.

Another aim of this study was to determinate adherence to the screening program and associations between

demographic factors and receipt of Pap smear. Of 423 patients who had a normal or benign initial Pap smear, 227 (53.7%) continued receiving Pap smears during the 5-year follow-up, and only 78 (34.4%) women received cervical cancer screening within 10 years. More than half of the immigrant women with a benign initial Pap smear did not repeat Pap smears during follow-up.

One potential explanation for these results is that these women came from countries with no screening programs and limited resources for disease prevention.[32]

Of the 11 HIV-positive women with cervical cancer, six (54.5%) had never undergone a Pap smear before their first visit to our center, and five (45.45%) had had a time interval between Pap smears of at least 4.2 years (range 2–5 years). As an AIDS-defining illness, cervical cancer poses a significant but preventable risk to HIV-infected women.[32]

The major limitation of our study is the retrospective, single-center approach. Rates of intra- or inter-variability of Pap smear reads and colposcopies were not determined. Examinations considering the oncogenic subtypes of HPV were not carried out and nor was a consideration of the association between cervical cancer in HIV-infected women and socioeconomic status.

In summary, management of HIV-positive women must be modeled on HIV-clinical status, CD4+ cell count, drug regimen, and adherence to follow-up, relying on the cooperation of highly qualified professionals. In HIV-positive women, an adequate screening and follow-up allows for a reduced occurrence of advanced cervical disease and prevents the recourse to invalidating surgical interventions.

Disclosure

The authors report no conflicts of interest.

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