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Abnormal Vaginal Pap Test After Hysterectomy in Human Immunodeficiency Virus–Infected Women

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Abstract

Objective—To evaluate the prevalence of abnormal vaginal cytology and vaginal intraepithelial neoplasia (VAIN) and vaginal cancer in human immunodeficiency virus (HIV)–infected women with no history of abnormal cytologic screening who had a hysterectomy for conditions other than cervical dysplasia and cancer; and to explore the risk factors associated with VAIN and vaginal cancer.

Methods—A retrospective cohort study was performed identifying 238 women between January 2000 to January 2015 with a history of HIV, previous hysterectomy, and no previous abnormal Pap tests. Medical records from patients with both HIV and history of hysterectomy were reviewed from Thomas Street Health Center and Northwest Community Health Center.

Results—Among 238 women, 164(69%) had normal Pap test results, 12(5%) had results showing atypical cells of undermined significance and human papillomavirus–positive, 55(23.1%) had results showing low-grade squamous intraepithelial lesion, and 7(2.9%) had results showing high-grade squamous intraepithelial lesion. No demographic risk factor was associated with abnormal Pap test after hysterectomy. Median follow-up time for the Pap test was 16 years. Of those who underwent vaginal biopsies for an abnormal Pap test, 15(28%) were normal, 23(43%) were VAIN1, 9(16%) were VAIN2, and 7(13%) were VAIN3. No patients had invasive vaginal cancer.

Conclusion—Over 30% of HIV-infected women who had no pre-hysterectomy history of an abnormal Pap test had abnormal vaginal Pap tests. Among those who had vaginal biopsies, 29%

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had VAIN2 or VAIN3, suggesting that Pap tests post-hysterectomy in the HIV population may be indicated.

Precis

Abnormal Pap tests are common after hysterectomy in women with human immunodeficiency virus infections without a history of cervical dysplasia.

Introduction

Pap test screening is an important component of primary care for women with human immunodeficiency virus (HIV) infection. In women without HIV infection, routine cytology screening for vaginal intraepithelial neoplasia (VAIN) and vaginal cancer after hysterectomy is not recommended if they have no history of cervical dysplasia.

Two guidelines have been published on Pap test screening in HIV-infected women after hysterectomy. The guideline by Department of Health and Human Services published in 2013 recommends a routine screening for HIV-infected women following a hysterectomy for high grade precancer or cervical cancer, however, it does not recommend a routine screening for those who underwent a hysterectomy for benign disease without history of high grade precancer or cervical cancer. A guideline published by the Infectious Disease Society of America suggests that HIV-infected women who have had a hysterectomy, especially those with a history of abnormal cervical cytology, should undergo regular screening with Pap tests, at intervals similar to those for women who have not undergone a hysterectomy(8). However, it remains unclear whether Pap test screening is not necessary for HIV-infected women after hysterectomy without a history of high grade precancer or cancer.

Our research aims to assess the prevalence of abnormal vaginal cytology and VAIN in HIV-infected women who had a hysterectomy for conditions other than cervical dysplasia or cancer. We also aim to explore the risk factors associated with vaginal dysplasia in women who had no cervical dysplasia prior to hysterectomy and the time to develop the abnormal Pap test.

Materials and Methods

This is a retrospective cohort study of HIV-infected women from two Harris Health System clinics, Thomas Street Health Center and Northwest Community Health Center, in Houston, Texas. These two sites have 68 providers, four of whom do Pap test screening; providers saw 1827 HIV-infected women in 2015. The rate of routine Pap test screening is 47%. Pap test screening was either done by physicians or nurse practitioners. The populations included in this study are HIV-infected women with no history of cervical dysplasia or cancer who have a history of hysterectomy and received routine gynecologic follow-up within the Harris Health System from January 2000 to January 2015. IRB approval was obtained through the Baylor College of Medicine Institutional Review Board and Harris Health System Institutional Review Board. Median follow-up time for the Pap test was 16 years.

Inclusion criteria included HIV-infected women with a history of hysterectomy for benign reasons without any history of cervical dysplasia or cervical cancer. Women may have had HIV diagnosed after hysterectomy. Cervical dysplasia is defined as having a record from personal report or from documented Pap test report in the medical record of atypical cells of undetermined significance and human papilloma virus positive (ASCUS and HPV+), low grade squamous intraepithelial lesions (LSIL), or high grade squamous intraepithelial lesions (HSIL) prior to hysterectomy or abnormal pathology report from hysterectomy. Exclusion criteria included HIV-uninfected women, HIV-infected women with a history of hysterectomy for cervical dysplasia or cervical cancer or with a pathology report from hysterectomy showing cervical dysplasia or cancer, and women with no Pap test information available after hysterectomy.

The electronic medical record for each patient was reviewed for date of birth, race and ethnicity, gravidity and parity, current or past smoking history, history of illicit drug use, history of alcohol abuse, date and age at hysterectomy, reason for hysterectomy, history of genital warts, cytology and pathology reports prior to hysterectomy, cytology results with date of each Pap test after hysterectomy, CD4 count (the number of CD4 T lymphocytes) at hysterectomy if available, viral load (the number of HIV particles per milliliter of blood) at hysterectomy if available, CD4 count within 6 months of each Pap test if available, viral load within 6 months of each Pap test if available, if on antiretroviral therapy at time of last Pap test, and vaginal biopsy results if available. Data were collected and coded on data collection form.

The Pap test results of ASCUS and HPV+, LSIL or HSIL after hysterectomy were defined as abnormal Pap tests, while Pap tests in categories Normal or ASCUS and HPV– were defined as normal Pap tests. Women were considered to be cases and have an abnormal vaginal Pap test if any Pap test was positive after hysterectomy. The proportion of cases and its asymptotic 95% confidence interval is used to estimate the prevalence of abnormal vaginal cytology.

Descriptive statistics, such as median, interquartile range (IQR, 25th, 75th percentile) for the continuous variables, frequency and proportion for the categorical variables were calculated for all patients and by groups. Viral load (VL) values were logarithm transformed for further data analysis.

Demographic and clinical characteristics were compared between cases and non-cases using Wilcoxon rank sum test for the continuous variables, and Chi-square test or Fisher's exact test for categorical variables.

We then used the Kaplan-Meier (KM) method to analyze the association between these factors and event free survival where the event is defined by the development of first abnormal Pap test after hysterectomy. The survival time is calculated by the duration in years between time of hysterectomy and date of first abnormal Pap test for the patients with any abnormal Pap tests after hysterectomy, and date of last clinical record for the patients with all normal Pap tests after hysterectomy. The KM curves were generated by levels of the factors and log rank tests were used to test the difference in the KM curves among strata.

Cox proportional hazard models were used to test the effect of risk factors on the survival using first category as reference group. Unadjusted and adjusted hazard ratios (HR) and their 95% CI were reported.

A p-value <0.05 was considered statistically significant. SAS software version 9.4 (SAS Institute, Cary, N.C.) was used for all analyses.

Results

The prevalence in this study of abnormal Pap tests after hysterectomy is 31% (95% CI: 25%, 37%). Among 238 women, Pap tests showed 12(5%) with ASCUS and HPV+, 55(23.1%) with LSIL, and 7(2.9%) with HSIL.

No specific demographic risk factor was identified as being associated with progression to vaginal dysplasia after hysterectomy (Table 1).

Of those who underwent vaginal biopsies for an abnormal Pap test, 15(28%) had normal biopsies, 23(43%) had VAIN1, 9(16%) had VAIN2, and 7(13%) had VAIN3. No patients had invasive vaginal cancer.

Race, smoking history, alcohol history, and illegal drug use were not associated with development of an abnormal Pap test (Table 1). No specific reason (bleeding, pelvic pain, uterine leiomyomas) for hysterectomy was associated with development of an abnormal Pap test.

Also, no historical obstetric or gynecologic demographic variable was associated with development of an abnormal Pap test (Table 2).

We calculated the effect size, and statistical power for the variables did not achieve the statistical significance in the tests. For example, the effect size of race, smoking, alcohol and drug use variables varies from 0.013 to 0.164 by the Chi-square tests. Per the general guideline suggested by Cohen, these effect sizes are small (small: 0.1, medium: 0.3, large: 0.5). With current sample size of 238, the statistical power to detect the difference between two groups varies from 5.3% to 61.6%. Larger sample sizes are needed to detect the significant difference for these small effect sizes.

The most recent CD4 count or viral load was not significantly different between abnormal and normal Pap tests, however the nearest CD4 count and viral load were significantly different between two groups (Table 3). Of note, patients with increased CD4 count or with decreased log of viral load were less likely to develop an abnormal Pap test, the p-values are 0.02 and 0.001 respectively (Figure 1,2). Patients who were younger at hysterectomy had longer period of time to develop an abnormal Pap test (Figure 3).

Adjusting other covariates, age and nearest viral load had significant effect on the abnormal Pap test free survival, while the effect of nearest CD4 count was not significant (p-value=0.14). More specifically, older patients and higher viral load significantly increased the risk of development of abnormal Pap test. For example, the patients with viral load

values greater than 400 had about 2 times of risk to develop abnormal Pap test than those lower than 400, the adjusted HR is 2.1 (95% CI: 1.2, 3.5) (Table 5).

No difference in time to abnormal Pap test was noted with ARV use ($p = 0.22$).

Discussion

Our findings suggest that a significant portion of HIV-infected women who have had a hysterectomy for benign reasons will have abnormal vaginal cytology and abnormal vaginal biopsies. Over 30% of HIV-infected women who had no pre-hysterectomy history of an abnormal Pap test had abnormal vaginal Pap tests. Among those who had vaginal biopsies, 29% had VAIN2 or VAIN3, suggesting that Pap tests post-hysterectomy in the HIV population may be indicated. No specific demographic risk factors were identified in women with abnormal cytology or VAIN. Pap test screening guidelines for HIV-infected women may need be modified in the future in response to the large number of abnormal vaginal cytological screening tests found.

Two other studies have similarly evaluated the incidence of abnormal Pap tests in HIV-infected women. A previous study by Paramsothy (2004) demonstrated that abnormal Pap tests were found among the HIV-infected population but only when no known Pap tests were performed or abnormal Pap tests had previously been documented. Massad (2012) investigated the Pap tests post-hysterectomy of 3700 HIV-seropositive women and concluded that although Pap tests were more often abnormal in HIV-seropositive women than HIV-seronegative women, VAIN 2 or worse was infrequent. Of note, the Massad study did not differentiate between the populations of women with abnormal cytology prior to hysterectomy and those with no history of an abnormal Pap test before hysterectomy. Our study specifically looked at those women who had no known history of abnormal cytology prior to surgery, a group that we might have presumed to be a low risk.

None of existing cytology screening guidelines specify whether cytologic screening of the vagina is indicated in women with HIV who have had hysterectomies for benign reasons. To date there has been little evidence to guide clinicians as to whether to continue Pap test screening in this population.

It is significant that in this study 31% of our patients had abnormal Pap tests and 29% of those women with vaginal biopsies had abnormal biopsies.

There was a statistically significant increase in the number of Pap tests in patients with history of normal Pap tests (normal or ASCUS and HPV-) versus those with history of abnormal Pap tests (ASCUS and HPV+, LSIL, or HSIL) ($p = 0.001$). No significant difference in the most recent CD4 count or viral load was found between those with normal versus abnormal Pap test. However, previous to the first abnormal Pap test, there was a statistically significant difference in the CD4 count ($p < 0.001$) and in the viral load ($p = 0.001$) between those with normal versus abnormal Pap test (Table 3).

We examined the number of CD4 count and VL available according to each Pap test. We have about 94% Pap tests with corresponding CD4 count and VL. The CD4 count and

VL chosen were those that were closest in time to the Pap test within a duration of 6 months; however the exact date was not recorded. This same interval of CD4 count and VL to Pap test was also used for the Pap test closest to hysterectomy, although due to lack of documentation at the time of hysterectomy before the patient entered the Harris Health System, this information was not always available.

More patients on antiretroviral therapy did have abnormal Pap tests ($p = 0.01$) but no significant difference was found in the grade of the Pap test if the patient was on antiretrovirals by the time of the abnormal Pap test ($p = 0.33$) (Table 4). We hypothesize that more abnormal Pap tests were found in the population of patients being followed in clinic on antiretroviral therapy because most of such patients receiving Pap tests were also being prescribed antiretroviral therapy.

Limitations of this study include sample size and retrospective study design which restricts the ability to control for variables and is dependent on the information documented in the patient's chart. The numbers were smaller than some previous studies because we purposely excluded women with prior abnormal Pap tests (guidelines do exist for the latter population). This study included patients from a single health system in a single demographic area and thus the findings may not be generalizable to other populations. Strengths of the study are the specific focus on HIV-infected women with no known pre-hysterectomy cytologic abnormality and the resulting addition to the previously scarce literature on this subject. Whether to focus on cytologic abnormalities (31% in this study) or high grade vaginal dysplasia (29% of those biopsied due to an abnormal Pap test and 6.7% of the total number of patients) remains to be determined.

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<250	45	33	15	9	1
250–399	40	31	13	8	2
≥400	147	98	57	25	4

Figure 1.
Abnormal Pap test-free survival by nearest CD4 count (cells/mm³).

Figure 2.
Abnormal Pap test-free survival by nearest human immunodeficiency virus (HIV) load.

<30	55	55	44	28	5
30–37	60	51	27	12	2
38–43	54	33	12	2	0
≥44	69	26	3	0	–

Figure 3.
Abnormal Pap test-free survival by age at time of hysterectomy.

Table 1
Demographic Information Among Patients with Abnormal and Normal Pap Tests

Variables	Category	Total	Normal n (%) 164	Abnormal n (%) 74	p- value
Race	White	18	13 (72.2)	5 (27.8)	0.93
	Black	187	129 (69)	58 (31)	
	Hispanic (non- white)	27	19 (70.4)	8 (29.6)	
	Other	2	1 (50)	1 (50)	
Smoker at hysterectomy	Current	113	73 (64.6)	40 (35.4)	0.20
	Former	10	9 (90)	1 (10)	
	No known history	115	82 (71.3)	33 (28.7)	
Smoker at most recent visit	Current	83	54 (65.1)	29 (34.9)	0.54
	Former	53	36 (67.9)	17 (32.1)	
	No known history	102	74 (72.5)	28 (27.5)	
Alcohol at hysterectomy	Current	78	55 (70.5)	23 (29.5)	0.90
	Former	3	2 (66.7)	1 (33.3)	
	No known history	157	107 (68.2)	50 (31.8)	
Alcohol at most recent visit	Current	78	59 (75.6)	19 (24.4)	0.05
	Former	23	11 (47.8)	12 (52.2)	
	No known history	137	94 (68.6)	43 (31.4)	
Drug use at hysterectomy	Current	53	37 (69.8)	16 (30.2)	1.00
	Former	6	4 (66.7)	2 (33.3)	
	No known history	179	123 (68.7)	56 (31.3)	
Drug use at most recent visit	Current	32	20 (62.5)	12 (37.5)	0.70
	Former	41	29 (70.7)	12 (29.3)	
	No known history	165	115 (69.7)	50 (30.3)	

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* Smoker = any use of tobacco products
† Normal Pap test = no abnormality or atypical cells of uncertain significance/human papilloma virus negative
‡ Abnormal Pap test = low-grade squamous intraepithelial lesions or high-grade squamous intraepithelial lesions
§ Alcohol use= any use of alcoholic drinks
|| Drug use= any use of illegal drugs
** p value obtained with Chi-square or Fisher's exact test

Obstetrics and Gynecology Historical Demographics Among Patients with Normal and Abnormal Pap Tests

Table 2

Continuous Variable	Normal, ASCUS/HPV –	Median (IQR)	ASCUS/HPV+, LSIL, HSIL	Median (IQR)	p-value
Age at hysterectomy	164	38 (30 – 45)	74	36 (30 – 44)	0.40
Gravida	157	3 (2 – 4)	73	2 (2 – 4)	0.60
Para	157	2 (1 – 3)	73	2 (1 – 3)	0.44
Abortions	157	0 (0 – 1)	73	0 (0 – 1)	0.59
Total number of Pap tests	164	2 (1 – 5)	74	4 (2 – 7)	0.001

* ASCUS = atypical cells of undetermined significance

[†] HPV = human papilloma virus

[‡] LSIL = low-grade squamous intraepithelial lesions

[§] HSIL = high-grade squamous intraepithelial lesions

^{||} p value obtained with Wilcoxon test

[¶] IQR = interquartile range

Table 3
HIV Historical Demographics Among Patients With Normal and Abnormal Pap Tests

Continuous Variable	Normal ASCUS /HPV–	Median (IQR)	ASCUS/HPV+, LSIL, HSIL	Median (IQR)	p-value
Last CD4	161	573 (354 – 738)	72	464 (307 – 696)	0.07
Last VL	160	48 (20– 512)	72	48 (20– 243)	0.28
Years from hysterectomy to last available clinical record	164	16 (8 – 25)	74	16 (11 – 28)	0.19
Nearest CD4 count before/on the first abnormal Pap test or last CD4 count	161	573 (354 – 738)	71	364 (213 – 529)	<0.001
Nearest VL before/on the first abnormal Pap test or last VL	160	248 (20– 512)	71	400 (48– 23271)	<0.001

* Last CD4 = last CD4 count during followup

[†] Last VL = last viral load during followup

[‡] p value obtained with Wilcoxon test

IQR = interquartile range

Table 4
Use of Antiretroviral Therapy Among Patients with Normal and Abnormal Pap Test

Categorical Variable	Category	Total	Normal n (%) 164	Abnormal n (%) 74	P value
On antiretroviral therapy any time after hysterectomy – Yes/ No	No	22	20 (90.9)	2 (9.1)	0.01
	Yes	200	130 (65)	70 (35)	
On antiretroviral therapy by first abnormal Pap test or any time after hysterectomy for normal patient – Yes/ No	No	31	20 (64.5)	11 (35.5)	0.33
	Yes	178	130 (73)	48 (27)	

* P value obtained with Chi square and Fisher exact test

Table 5

Unadjusted and adjusted hazard ratio (HR) and 95% confidence interval (CI) examining the association between Age, CD4 count, and Viral Load and development of abnormal Pap test

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Age <30	Ref	ref
Age 30– <38	2.26 (1.19, 4.28)	2.22 (1.16, 4.26)
Age 38–<44	3.62 (1.72, 7.64)	3.78 (1.75, 8.16)
Age>=44	6.33 (2.98, 13.43)	6.26 (2.91, 13.47)
CD4 <250	Ref	ref
CD4 250–<400	0.87 (0.46, 1.64)	1.03 (0.54, 1.96)
CD4 <=400	0.48 (0.28, 0.83)	0.61 (0.34, 1.10)
Viral load <400	Ref	ref
Viral load >=400	2.35 (1.44, 3.84)	2.07 (1.24, 3.47)

• CD4 = CD4 count