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Vaginal intraepithelial neoplasia in patients after total hysterectomy

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ABSTRACT

Objectives: To investigate the incidence of vaginal intraepithelial neoplasia (VaIN) after total hysterectomy and, subsequently, optimize the follow-up strategy of patients after hysterectomy.

Methods: This retrospective study was conducted on 8581 patients with benign gynecology disease who underwent total hysterectomy in our institution between January 2006 to December 2017, including 834 patients with cervical intraepithelial neoplasia (CIN) and 7747 patients without cervical lesions before hysterectomy. All patients underwent postoperative high-risk human papilloma virus (Hr-HPV) screening and liquid-based cytology test (LCT) as confirmatory tests. Colposcopies were performed if the results of the confirmatory tests were abnormal, and biopsies were performed depending on colposcopy images. The mean follow-up time was 33.8 ± 12.1 months. The relationship among VaIN, CIN, and confirmatory test results was investigated.

Results: VaIN was found in 81 patients after hysterectomy (incidence rate, 0.9%). The incidence rates of VaIN in patients with and without CIN history were significantly different (7.3%, 61/834, vs 0.3%, 20/7747; $P < 0.05$). Compared with patients without CIN history, those with CIN history were more likely to have abnormal LCT results in the postoperative follow-up, especially low-grade squamous intraepithelial lesions or worse ($P < 0.001$). Patients with high-grade squamous intraepithelial lesions in the LCT have a high VaIN incidence (patients with CIN history, 57.1%; patients without CIN history, 15.1%), and the 2 patients

Abbreviations: AC, adenocarcinoma; AGC, atypical glandular cells; ASCCP, American Society of Colposcopy and Cervical Pathology; ASC-H, atypical squamous cells, cannot exclude a high-grade squamous intraepithelial lesion; ASC-US, atypical squamous cells of unknown significance; CIN, cervical intraepithelial neoplasia; Hr-HPV, high-risk human papilloma virus; HSIL, high-grade squamous intraepithelial lesion; LCT, liquid-based cytology test; LSIL, low-grade squamous intraepithelial lesion; SCC, squamous cell carcinoma; VaIN, vaginal intraepithelial neoplasia.

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with squamous cell carcinoma or adenocarcinoma (SCC/AC) in the LCT had CIN and VaIN or worse after hysterectomy. The Hr-HPV infection rates after the hysterectomy of patients with and without CIN history were 18.8% (157/834) and 5.4% (419/7747), respectively. The incidences morbidities of VaIN in patients with persistent Hr-HPV infection and in those with and without CIN history were 35.7% and 12.0%, respectively, and were significantly higher than those in patients with negative Hr-HPV (patients with CIN history, 0.7%; patients without CIN history, 0.1%; $P = 0.002$). The incidence of VaIN in patients with CIN history with HPV-16 infection after hysterectomy was as high as 50%, but in patients without CIN history, the incidences of different Hr-HPV subtypes were not significantly different ($P = 0.953$).

Conclusion: Patients with CIN history were more prone to VaIN and SCC after hysterectomy than were patients without CIN history. Patients should be screened thoroughly for cervical and vaginal lesions before hysterectomy. After hysterectomy, patients with CIN history should undergo lifetime annual LCT and HPV screening.

ARTICLE INFO

Keywords: Vaginal intraepithelial neoplasia; Hysterectomy; High-risk human papillomavirus; Liquid-based cytology

Introduction

Vaginal intraepithelial neoplasia (VaIN) is a series of precancerous lesions of vaginal squamous cell carcinoma (SCC). It was reported that 5% of cases may progress from occult focus to invasion in spite of the close follow-up.[1] Latent cancers have been reported in 6.8%-18.6% of patients with high-grade squamous intraepithelial lesions (HSILs).[2,3] Early diagnosis and timely treatment of VaIN can reduce the incidence of vaginal cancer.[4-6] Influenced by traditional beliefs, after hysterectomy, Chinese women generally do not undergo the follow-up disease screening of their reproductive system. Furthermore, due to the lack of specific symptoms and the limitation of the vaginal structure, the diagnosis of VaIN is easy to be missed or is delayed, especially for patients who underwent hysterectomy. Some researchers even encouraged the prevention of unnecessary screening for women who have undergone hysterectomy.[7] At present, the natural course of VaIN is not completely clear, and international guidelines on VaIN after hysterectomy are lacking. According to the detecting strategy for cervical intraepithelial neoplasia (CIN), the liquid-based cytology test (LCT) and high-risk human papilloma virus (Hr-HPV) are the usual confirmatory tests, and biopsy under colposcopy is the gold standard. The purpose of this study was to analyze the clinical characteristics and incidence of VaIN in patients after hysterectomy and to provide a basis for the follow-up of the residual vagina in patients after hysterectomy, especially those who underwent hysterectomy due to cervical lesions.

Materials and methods

Recruitment patients

This retrospective study included patients who underwent total hysterectomy from January 2006 to December 2017 at the Center for Cervical Disease of the International Peace Maternity and Child Health Hospital. The inclusion criteria were hysterectomy due to benign gynecological diseases (eg, CIN, uterine leiomyoma, adenomyosis, benign ovarian cyst), postoperative pathology not indicative of a malignant tumor, follow-up in our hospital, and with at least one follow-up at the first year after hysterectomy. The exclusion criteria were a malignant tumor of the female reproductive system or with other systemic malignancies, lost to follow-up after hysterectomy,

followed-up in another hospital, and incomplete clinical data. This study was approved by the institutional ethics committee (IPM-2018-18). All patients provided written informed consent.

Hysterectomy and follow-up strategy

The surgical approaches of all the hysterectomies included abdominal hysterectomy, laparoscopic hysterectomy, vaginal hysterectomy, and laparoscopically assisted vaginal hysterectomy. Follow-up confirmatory strategy included the LCT and/or HPV screening, and colposcopy was performed if the confirmatory tests showed abnormal results; biopsies were performed depending on the colposcopy images. The first follow-up of VaIN was performed at the first year after hysterectomy, and then patients were followed up every 1-3 years according to their primary diseases.

Confirmatory LCT and Hr-HPV screening

LCT was performed for cytological examination of the residual vagina, and the Bethesda System standard 2001 was used for the cytological classification: (1) Normal; (2) atypical squamous cells of unknown significance (ASC-US); (3) atypical glandular cells (AGCs); (4) atypical squamous cells, cannot exclude an HSIL (ASC-H); (5) low-grade squamous intraepithelial lesion (LSIL); (6) high-grade squamous intraepithelial lesion (HSIL); (7) squamous cell carcinoma (SCC); and (8) adenocarcinoma (AC). The proportion of ASC-US diagnosis is no more than 2-3 times of squamous intraepithelial lesions. Abnormal LCT refers to a result of ASC-US/AGC or worse.

Before July 2014, only a second-generation hybrid capture assay (Hybrid Capture II) was used to detect 13 high-risk types of HPV (HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59, and HPV-68). HPV DNA $\geq$ 1 pg/mL was considered a positive result. Since July 2014, the Cobas 4800 high-risk HPV testing system (Roche Diagnostics, Basel, Switzerland) was also used to detect Hr-HPV and gradually became the main testing system. The results showed the qualitative results of HPV-16, HPV-18, and the other 12 high-risk HPV subtypes (including HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59, HPV-66, and HPV-68).

The results of the LCT and/or Hr-HPV test were referred to the results at the last follow-up or when VaIN was diagnosed.

Colposcopy and pathological examination

Colposcopies were performed when confirmatory test results were abnormal. Suspicious lesions were biopsied depending on the colposcopy images after acetic acid and iodine reagent staining, respectively. All colposcopy operations were performed by 8 qualified colposcopy specialists in our center. The pathology results were classified as normal, VaIN1, VaIN2, VaIN3, or vaginal SCC.

Statistical analysis

SPSS version 23.0 (IBM Corp., Armonk, NY, USA) was used for the data analysis. Quantitative data are summarized as means with standard deviations. The *t* test was used for the comparison of normally distributed data. Count data are summarized as numbers with percentages and were compared using the chi-square test. $P < 0.05$ was considered statistically significant.

Table 1
Clinical features of the patients.

	Total (n = 8581)	With CIN history (n = 834, 9.7%)	Without CIN history (n = 7747, 90.3%)	*P*-value
Age (y)	53.0 ± 7.6 [32-76]	54.3 ± 7.3 [32-73]	52.9 ± 7.8 [43-76]	0.071
Menstrual status				0.004
Premenopausal	5955 (694)	542 (65)	5413 (69.9)	
Postmenopausal	2626 (30.6)	292 (35)	2334 (30.1)	
Average gravidity	2.3	2.5	2.3	0.035
Parity	1.1	1.3	1.1	<0.001
Follow-up time (mo)	33.8 ± 12.1	44.5 ± 14.7	32.6 ± 11.8	<0.001
No. of follow-up times	2.95	3.4	2.9	<0.001
Indication of hysterectomy				<0.001
CIN	766	776 (93)	0	
Uterine leiomyoma	3603	25 (3)	3578 (46.2)	
Adenomyosis	2870	16 (1.9)	2854 (36.8)	
Uterine prolapse	856	9 (1.1)	847 (10.9)	
Abnormal uterine bleeding	366	5 (0.6)	361 (4.7)	
Others	110	3 (0.4)	107 (1.4)	

Data are presented as mean ± standard deviation, (range), or n (%).

Table 2
Relationship between VaIN after hysterectomy and CIN history.

VaIN after hysterectomy	With CIN history		Without CIN history		Chi-square	*P*-value
	Cases	Incidence	Cases	Incidence		
VaIN or SCC (n = 81)	61	7.3	20	0.3	17.422	<0.001
VaIN1 (n = 27)	17 (27.9)	2.0	10 (50)	0.1	20.223	<0.001
VaIN2 (n = 16)	13 (21.3)	1.6	3 (15)	0.0		
VaIN3 (n = 35)	28 (45.9)	3.4	7 (35)	0.1		
SCC (n = 3)	3 (4.9)	0.4	0	0		

Data are presented as n (%).

Results

Clinical features of the patients

A total of 8581 patients were included in this retrospective study. The patients' clinical characteristics are presented in Table 1.

Relationship between VaIN or vaginal carcinoma after hysterectomy and CIN history

A total of 81 patients were diagnosed with VaIN (78 cases) or SCC (3 cases) after hysterectomy, including 61 with CIN history and 20 without CIN history (Table 2). The incidence of VaIN or worse in patients after hysterectomy was 0.9% (81/8581). The incidence rate of VaIN was significantly higher in patients with CIN history (7.3%) that in patients without CIN history (0.3%; $P < 0.001$). The results of the Fisher exact test suggested that patients with CIN history before hysterectomy were more likely to have high-grade VaIN or vaginal carcinoma after hysterectomy than patients without CIN ($P < 0.001$). The incidence of VaIN in patients without CIN history before hysterectomy was low, and such lesions were less likely to develop into vaginal carcinoma. The interval time from hysterectomy to VaIN or vaginal cancer was 12.8 months (range, 6-67 months).

Table 3
Relationship between VaIN after hysterectomy and follow-up LCT.

	With CIN history			Without CIN history			*P*-value
	Cases	VaIN or worse	Incidence (%)	Cases	VaIN or worse	Incidence (%)	
Total	834	61	7.3	7747	20	0.3	<0.001
Normal	645 (77.3)	6	0.9	7127 (92)	7	0.1	<0.001
ASC-US/AGC	34 (4.1)	6	17.6	481 (6.2)	6	1.2	<0.001
LSIL	125 (15)	31	24.8	106 (1.4)	2	1.8	<0.001
HSIL/ASC-H	28(3.4)	16	57.1	33 (0.4)	5	15.1	0.001
SCC/AC	2 (0.2)	2	100	0	-	-	-

Data are presented as n (%).

Table 4
Relationship between VaIN or vaginal carcinoma after hysterectomy and Hr-HPV infection.

HPV after hysterectomy	With CIN history			Without CIN history			*P*-value
	Cases	VaIN or worse	Incidence (%)	Cases	VaIN or worse	Incidence (%)	
Negative	677(81.2)	5	0.7	7328(94.6)	7	0.1	0.002
Positive	157(18.8)	56	35.7	419(5.4)	13	3.1	<0.001
HPV-16	34(4.1)	17	50.0	67(0.9)	2	3.0	<0.001
HPV-18	18(2.3)	7	38.9	24(0.3)	1	4.2	0.013
Unknown or other subtypes	105(12.6)	34	32.4	328(4.2)	10	3.0	<0.001

Data are presented as n (%).

Relationship between VaIN after hysterectomy and follow-up LCT

After hysterectomy, more than 90% of the patients (7772/8581) had normal follow-up LCT results, and in these patients, the incidence of VaIN was only 0.2% (13/7772). In patients with a negative LCT and without CIN, the incidence of VaIN after hysterectomy was as low as 0.1%, which was significantly lower than that in patients with CIN history before hysterectomy (Table 3). Compared with patients without CIN history, patients with CIN history were more likely to have abnormal LCT results in the postoperative follow-up ($P < 0.001$), and the proportions of LSIL and HSIL (HSIL/ASC-H) were significantly higher. Even with the same LCT results, the incidence of patients with CIN history was higher than that of patients without CIN history, which suggests that the LCT has a higher value in the follow-up of patients with CIN history after hysterectomy ($P < 0.05$). Meanwhile, 57.1% of patients with CIN history and HSIL in the LCT were detected to have VaIN or worse, and the 2 patients with CIN history and SCC/AC in the LCT were both detected to have VaIN or worse, which suggests that the follow-up LCT of high-grade lesions strongly predicts occurrence of VaIN in patients with CIN history after hysterectomy.

Relationship between VaIN after hysterectomy and persistent Hr-HPV infection

The HPV infection rate was significantly higher in patients with CIN history than that in patients without CIN history after hysterectomy (Table 4). The incidence of VaIN in patients with persistent Hr-HPV infection was significantly higher than those in patients with negative Hr-HPV after hysterectomy. In patients with CIN history, HPV-16 infection after hysterectomy indicated an incidence of VaIN as high as 50%. However, in patients without CIN history, the incidences of patients with different Hr-HPV subtypes were not significantly different. The HPV subtype test had higher value in patients with CIN history. VaIN was more likely to be detected at the follow-up after hysterectomy in patients with CIN history with the same HPV results ($P < 0.05$).

Discussion

VaIN accounts for 0.4% of lower genital tract intraepithelial diseases, and it can affect women of all ages and is more common in those with immunosuppression.[8] It is believed that the occurrence of VaIN is related to HPV infection, CIN or cervical cancer history, previous hysterectomy, immunosuppression, pelvic radiotherapy, and other factors.[9,10]

VaIN after hysterectomy

Approximately 86.8% of VaIN occurs at the upper third of the vagina,[11] and the most common finding under colposcopy was the presence of acetowhite epithelium.[12] Because of the concealed site of the disease, vaginal lesions can be easily missed by cytology, HPV test, and colposcopy, and its true incidence is difficult to assess. Many previous studies have proposed that previous hysterectomy was a high-risk factor for VaIN.[13] Sopracordevole et al[14] found that women with high-grade VaIN and previous hysterectomy had a significantly higher incidence of invasive vaginal cancer than non-hysterectomized women (16.7% vs 1.4%; $P < 0.0001$). In this study, we found that the incidence of patients with CIN history was significantly higher than that of patients without CIN history, and the incidence rate of VaIN in patients without CIN history was exceptionally low (0.3%). We believe that VaIN is only related to hysterectomy in patients with CIN history, but precancerous lesions of the remaining part of the vagina after hysterectomy are exceedingly rare in patients without CIN history. The American Society of Colposcopy and Cervical Pathology recommends that the screening of the vagina after hysterectomy should only be done in women with CIN2 or worse,[15] and our results basically support this strategy.

Relationship between VaIN after hysterectomy and CIN history

In recent years, as HPV and cytology screening increased, the detection rates of CIN increased as well. Total hysterectomy is widely used in high-risk patients without fertility requirements. However, Schockaert et al[16] reported that hysterectomy may not be a definitive therapy for CIN2+ because the incidence rate of subsequent VaIN2+ is as high as 7.4%. In this study, we obtained a similar incidence rate (7.3%) in patients with CIN history after hysterectomy. Many studies have proven that the occurrence of VaIN is closely related to CIN.[1,14,17] Zhang et al[18] found that approximately half of VaIN cases were diagnosed during the follow-up of CIN and speculated that VaIN may be the progression of CIN and may also be residual lesions. This suggests that we should pay special attention to the vagina during colposcopy in patients with CIN. In procedures of loop electrosurgical excisional procedure or total hysterectomy, we should deal with the focus of the vagina as much as possible to reduce the residual of VaIN.

Follow-up LCT and VaIN after hysterectomy

LCT, as a cytological test, is widely used in the screening of female lower genital tract lesions for years. In a retrospective study, Cong et al[2] observed that 90.7% of patients with VaIN2 or worse had an abnormal LCT after hysterectomy. From the multivariate analysis, Shen et al[19] confirmed that the HSILs of the LCT were associated with the persistence/recurrence of vaginal HSIL post-hysterectomy (odds ratio: 25.45, $P = 0.00$). Gunderson et al[20] reported that the cytology results of HSIL or AGC revealed VaIN2 or VaIN3 in 89% of the cases ($P = 0.0019$) and VaIN1 in 53% of the cases. Owing to the high risk of recurrence and progression, patients with VaIN2 and VaIN 3 should undergo LCT evaluation.[21] In our study, the positive predictive values of the LCT result of HSIL in patients with CIN history was $\geq$50% (57.1% and 100%). Women with abnormal vaginal cytology have a high incidence of vaginal dysplasia, especially in those with CIN

history. However, the degree of dysplasia is not completely consistent with the reference cytology,[20] which may be due to vaginal adhesion and scar healing post-hysterectomy. As the LCT is an effective, but limited, screening method for VaIN after hysterectomy, it should be included in the follow-up strategy of these patients.

Follow-up Hr-HPV screening and VaIN after hysterectomy

Persistent infection of Hr-HPV is associated with high-grade intraepithelial lesions and invasive cancer of the lower genital tract. Smith et al[22] reported that HPV was detected in 65.5% of vaginal cancer, 92.6% of VaIN2/3, and 98.5% of VaIN1 patients. In this study, 18.8% of patients with CIN history have persistent Hr-HPV infection after hysterectomy, and positive HPV results after hysterectomy indicate a 35.7% incidence of VaIN. The positive predictive value of HPV-16 is as high as 50% in these patients. In patients without CIN history, the infection rate of HPV was significantly lower (4.5%), and the incidence rate of VaIN in HPV-positive patients was also significantly lower (3.1%). According to this, we speculate that HPV infection after hysterectomy is temporary in patients without CIN history, but it may be the continuation of the cervical etiology in patients with CIN history. Chao et al[23] found that 58.7% of VaIN patients detected the concordant HPV types with concomitant CIN, and the shorter the interval time between CIN and VaIN, the more likely were they caused by the same type of HPV. Multiple HPV infections were found in 42.9% of the VaIN patients.[18] The vagina is likely a reservoir of HPV, which causes both CIN and VaIN. However, only HPV-16 is the main virus type to be associated with the progression and recurrence of VaIN.[4,10,22] After hysterectomy, patients should undergo follow-up Hr-HPV screening, especially those with CIN history.

Follow-up strategy for VaIN after hysterectomy

The time of progression from VaIN to invasive vaginal cancer is not completely consistent in various studies. Hodeib et al[21] reported that the median time from VaIN to develop to the invasive cancer of the lower genital tract was 64 months (range, 30–101 months). Gunderson et al[20] reported a shorter median time of 17 months for VaIN1, 11 months for VaIN2, and 11 months for VaIN3 ($P = 0.036$). However, Zeligs et al[24] found that 89% of patients demonstrated normalization of VaIN, with a median time of 15.9 months from low-grade VaIN and 10.0 months from high-grade VaIN. In this study, the interval time from hysterectomy to VaIN or vaginal cancer was 12.8 months (range, 6-67 months). Based on these research results, we recommend a follow-up strategy that includes the LCT and HPV screening every year after hysterectomy for patients with CIN history. Because of the uncertain development and much longer interval time reported in other studies,[9,20] we recommended lifetime follow-up. For patients without CIN history, the incidence of high-grade VaIN and vaginal carcinoma is rare after comprehensive cervicovaginal assessment before surgery. The follow-up strategy for these patients can be similar to that of the general population (screening every 3 years until the age of 65 years).

Limitations

The progress of VaIN is slow and the patients' awareness of the need of follow-up after hysterectomy is relatively low; thus, it is difficult to achieve a satisfactory follow-up time and frequency. In our study, 2137 patients (20.7%) have never been followed up in our hospital, and considering the long progression duration, the mean follow-up time of this study was short.[20] Since it is difficult to standardize the treatment and follow-up of VaIN, the diagnosis of VaIN was defined as the end point of observation, whether it was VaIN1 or worse. The trend of progression of VaIN1 to true neoplastic VaIN is difficult to predict. The research on the outcome

of VaIN needs prospective study design and observation. Besides, further studies are needed to determine whether the optimization of the follow-up strategy of VaIN after hysterectomy can change the outcome of vaginal cancer.

Conclusion

Patients with CIN history were more prone to the VaIN and SCC of the vagina after hysterectomy than were patients without CIN history. Cervical and vaginal lesions should be screened thoroughly before hysterectomy. Abnormal LCT results and persistent Hr-HPV infection are important predictors of VaIN after hysterectomy. Thus, patients with CIN history after hysterectomy should undergo lifetime annual follow-up LCT and HPV screening.

CRediT authorship contribution statement

Dan Cao: Conceptualization, Methodology, Software, Formal analysis, Writing - original draft. **Dan Wu:** Methodology, Data curation, Formal analysis, Funding acquisition, Writing - original draft. **Ying Xu:** Conceptualization, Investigation, Validation, Writing - review & editing.

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