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ORIGINAL RESEARCH

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A retrospective study of 657 women with vaginal intraepithelial neoplasia (VaIN)

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Abstract

Vaginal intraepithelial neoplasia (VaIN) is frequently underdiagnosed. The aim of this study was to explore the clinical characteristics of patients with VaIN and identify more sensitive diagnostic methods. This study retrospectively analyzed 657 patients with VaIN from the International Peace Maternal and Child Health Hospital during a ten-year period. Among the 657 patients, 26.5% were diagnosed with VaIN 2/3. The proportions of patients with VaIN 2/3 among those who did and did not undergo hysterectomy were 39.5% and 24.7%, respectively. The sensitivity of cytology testing for VaIN in those with only VaIN, VaIN concomitant with cervical or vulvar lesions, and posthysterectomy VaIN was 56.7%, 66.5%, and 72.3%, respectively. The sensitivity of high-risk human papillomavirus (hrHPV) testing for VaIN in the same categories was 87.7%, 86.5%, and 74.3%, respectively. The sensitivity of cytology and hrHPV cotesting for VaIN in the same categories was 95.2%, 95.6%, and 95.0%, respectively. In patients with VaIN 2/3, the incidence of HPV 16/18 was 50.6%. However, in patients with VaIN 1, the incidence of HPV 16/18 was only 22.6 %. The severity of VaIN was associated with HPV genotyping and hysterectomy, but not with concomitant cervical or vulvar lesions. A combination of cytology and hrHPV could increase the sensitivity of the diagnosis of VaIN. HPV 16 and 18 are the most frequent HPV-types in VaIN 2/3. Twelve specific hrHPV subtypes were the main virus types associated with the development of VaIN 1.

Keywords

Carcinoma *in situ*; Human papilloma viruses; Hysterectomy; Vaginal neoplasms

1. Introduction

Vaginal cancer is rare, constituting only 1–2% of all female genital tract malignancies [1]; although rare, vaginal cancer is increasing in prevalence owing to the increase in persistent HPV infections. Vaginal intraepithelial neoplasia (VaIN) is a premalignant disease that may lead to vaginal cancer. Similar to cervical intraepithelial lesion (CIN), there are three different subgroups of VaIN: vaginal low-grade squamous intraepithelial lesion (LSIL/VaIN1) and vaginal high-grade squamous intraepithelial lesion (HSIL/VaIN 2/3) subgroups.

Compared with non-hysterectomized women in the general population, hysterectomized women have a more than doubled risk of contracting vaginal cancer [2]. Cao *et al.* [3] reported that patients with a CIN history were more prone to VaIN and vaginal cancer after hysterectomy than patients without a CIN history. Recent research has shown that hysterectomized women with prevalent CIN at the time of surgery have a high risk of subsequent vaginal cancer. This risk remains elevated for at least 15 years [2].

VaIN is frequently underdiagnosed. Except for a small number of patients who report postcoital spotting or unusual vaginal discharge, most patients have no obvious symptoms. In recent decades, with the development of cervical cancer screening methods, such as cytology, high-risk human papillomavirus (hrHPV) testing, and colposcopy, the diagnosis of VaIN has increased steadily. However, owing to the rarity of VaIN, data on cytology, hrHPV testing, and colposcopy results associated with VaIN are limited. Few studies have focused on the role of HPV infection in vaginal HSILs; however, data on the HPV detection rate in VaIN samples are conflicting. Chao *et al.* [4] reported that the HPV detection rate in VaIN was 69.3%, while other studies showed a higher detection rate of 90–100% [5, 6].

Given the limited study on cytology, HPV genotypes of VaIN patients, we decided to retrospectively recruited 657 patients who had a histopathological diagnosis of VaIN to understand the clinical characterization of VaIN, including the distribution of VaIN 1 and VaIN 2/3 and the results of cytology and hrHPV results.

2. Materials and Methods

We performed a retrospective study from 01 January 2009, until 31 December 2019. Data were collected from the electronic database of the International Peace Maternal and Child

Health Hospital. All women with an initial histopathological diagnosis of VaIN according to two independent pathologists were included. Patient demographics and clinical information, including histological information, cytology, and hrHPV testing results were recorded. ThinPrep cytology test (TCT) screening was carried out using a ThinPrep 2000 Processor (HOLOGIC, New York, NY, USA). The Bethesda 3-tier system was used as the cervical cytological diagnostic criteria. Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesions (ASC-H), LSILs, HSILs, or squamous cell carcinoma (SCC), were regarded as abnormal TCT results. HPV status was determined by using the Cobas 4800 Human Papillomavirus (HPV) Test. The test utilizes amplification of target DNA by polymerase chain reaction (PCR) and nucleic acid hybridization for the detection of 14 high-risk HPV types in a single analysis. The test specifically identifies (types) HPV16 and HPV18 while concurrently detecting the rest of the high risk types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) at clinically relevant infection levels. The Institutional Review Board (IRB) of the International Peace Maternal and Child Health Hospital approved this study. Data were analyzed using Statistical Package for Social Sciences (SPSS) version 17.0 (SPSS Inc., Chicago, IL, USA). Differences were considered statistically significant if $p < 0.05$. 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.

3. Results

Among the 657 patients, 26.5% were diagnosed with VaIN 2/3, and 73.5% were diagnosed with VaIN 1. The mean age of the LSIL group was 50.65 (range, 18–74) years; the mean age of the HSIL group was 50.54 (range, 21–79) years. The p value was 0.9213. A total of 657 cases of VaIN were classified as shown in Table 1. In total, 76.0% of the patients had only VaIN, including 132 with HSILs and 367 with LSILs; 24.0% had concomitant cervical or vulvar lesions.

Among the 576 patients without a history of hysterectomy, 24.7% were diagnosed with VaIN 2/3, and 75.3% were diagnosed with VaIN 1. A total of 72.6% of the patients were diagnosed with only VaIN and 27.4% were diagnosed with VaIN concomitant with cervical or vulvar lesions. Among the patients with only VaIN, 23.9% were diagnosed with VaIN 2/3. Among those with concomitant VaIN, 26.6% were diagnosed with VaIN 2/3. The proportion of patients with VaIN 2/3 among the patients with concomitant cervical lesions was similar to that among the patients with only VaIN ($p = 0.5169$).

Among 81 patients with a history of hysterectomy, 39.5% were diagnosed with VaIN 2/3. The proportion of patients with VaIN 2/3 among the patients who underwent hysterectomy (39.5%) was higher than that among the patients who did not undergo hysterectomy (24.7%) ($p = 0.0068$) (Table 2).

A complete history was available in 81 patients with VaIN after hysterectomy. Table 3 shows the indications for previous hysterectomy in patients with VaIN. Among the patients with previous hysterectomy, 66.7% underwent hysterectomy for cervical lesions, including cervical cancer (48.1%) and precancerous (51.9%) lesions. A total of 33.3% underwent hysterectomy for noncervical lesions, including uterine fibroid (40.8%), endometrial cancer (22.2%), ovarian cancer (22.2%), fallopian tube cancer (3.7%) and adenomyosis (11.1%).

The cytology reports for 657 patients are shown in Table 4. The patients were grouped according to the history of hysterectomy. Cytology reports of VaIN were based on the Bethesda system (TBS) cytology classification. In 576 patients with VaIN without hysterectomy, cytology sensitivity was 60.0%; among these patients, cytology sensitivity for VaIN 2/3 and VaIN 1 was 68.3% and 56.7%, respectively. Among 76 patients after hysterectomy, cytology sensitivity for all patients was 72.3%, and that for VaIN 2/3 patients was 80.0%.

The available hrHPV testing reports for 657 patients with

TABLE 1. Original composition of vaginal, cervical, and vulvar lesions.

Vagina	Cervix	Vulva	Number
HSIL	/	/	132
HSIL	Cancer	/	14
HSIL	HSIL	/	14
HSIL	LSIL	/	12
HSIL	/	HSIL	1
HSIL	HSIL	LSIL	1
Total			174 (26.5%)
LSIL	/	/	367
LSIL	CA	/	7
LSIL	HSIL	/	16
LSIL	LSIL	/	92
LSIL	/	HSIL	1
Total			483 (73.5%)

HSIL: high-grade squamous intraepithelial lesion; LSIL: low-grade squamous intraepithelial lesion; / indicates no lesion.

TABLE 2. VaIN diagnosed after hysterectomy or with no hysterectomy.

VaIN	N	Proportion
No hysterectomy	576	100%
VaIN 2/3	142/576	0.247
VaIN 1	434/576	0.753
Only vaginal lesions	418/576	0.726
VaIN 2/3	100/418	0.239
VaIN 1	318/418	0.761
Concomitant lesions	158/576	0.274
VaIN 2/3	42/158	0.266
VaIN 1	116/158	0.734
After hysterectomy	81	100%
VaIN 2/3	32/81	0.395
VaIN 1	49/81	0.605

VaIN: vaginal intraepithelial neoplasia.

TABLE 3. Indications for previous hysterectomy in patients with VaIN.

Indications for hysterectomy	VaIN	VaIN 2/3	VaIN 1
Cervical lesions	54	26	28
Cervical cancer	26	11	15
Cervical precancer	28	15	13
Noncervical lesions	27	6	21
Endometrial cancer	6	2	4
Fallopian tube cancer	1	1	0
Ovarian cancer	6	1	5
Uterine myoma	11	2	9
Adenomyosis	3	0	3
Total	81	32	49

VaIN: vaginal intraepithelial neoplasia.

VaIN were classified as shown in Table 4 and Table 5. Among 576 patients with VaIN without hysterectomy, the frequency of hrHPV infection was 89.30% for VaIN 2/3 and 86.8% for VaIN 1. Among 81 patients with VaIN after hysterectomy, for VaIN 2/3, the frequency of hrHPV infection was 93.3%; however, the frequency of hrHPV infection for VaIN 1 was only 62.50%. HPV genotyping is significantly different in patients with VaIN 1 and VaIN 2/3. In patients with VaIN 1, the incidence of 12 specific hrHPV subtypes was as high as 73.2%. However, in patients with VaIN 2/3, HPV16 and/or HPV18 is the main virus type, accounting 50.6%.

Cytology/hrHPV cotesting reports were available for 657 patients with VaIN (Table 4). Cotesting reports were available in 576 patients with VaIN and no history of hysterectomy, and the sensitivity of cotesting for all VaIN, VaIN 1, and VaIN 2/3 patients was 95.0%, 94.9%, and 96.5%, respectively. In 81 patients with VaIN after hysterectomy, the sensitivity of cotesting for all VaIN, VaIN 1, and VaIN 2/3 patients was 95.0%, 93.8%, and 97.0%, respectively.

4. Discussion

VaIN is a precancerous condition of the lower genital tract and accounts for 0.4% of all lower genital tract precancerous lesions. The incidence of VaIN was 0.2–2/100,000 and as the HPV infection rate increased, cervical fluid-based cytology improved, HPV detection and colposcopy increased, and the incidence of VaIN increased [7]. The Hospital of Obstetrics and Gynecology affiliated with Fudan University reported that the detection rate of VaIN via colposcopy over the course of 2 years reached 2.58% [8]. Because of its rarity, to date, there is no standardized guidance for VaIN. In our study, during a 10-year period, 657 patients with a histopathological diagnosis of VaIN were retrospectively included. Among 657 patients, 26.5% were diagnosed with VaIN 2/3. A total of 73.5% were diagnosed with VaIN 1.

The pathogenesis of VaIN is unclear, and some researchers believe that VaIN is the result of the progression of CIN. VaIN usually coexists with CIN rather than in isolation [9]. In the Dodge study, 65% of patients with VaIN had CIN, but there are also many lreports in which the proportion of patients with only VaIN is also large [10]. Sui *et al.* [8] reported that the proportion of VaIN patients with CIN ranged from 29.58% to 33.83%. Similarly, in our study, 72.6% were diagnosed with only VaIN, and 27.4% were diagnosed with VaIN concomitant with cervical or vulvar lesions. We suggest that VaIN may have been isolated and not necessarily associated with cervical/vulvar disease. Ao *et al.* [11] reported that the ratio of patients with VaIN with concomitant neoplasia of the lower genital tract increased with the grade of VaIN. In our study, the ratio of VaIN 2/3 was similar in concomitant VaIN with in only VaIN (p = 0.5169), suggesting that the proportion of VaIN 2/3 was not affected by cervical or vulvar lesions. These results indicated that the vagina could be the first site of neoplasia in the lower genital tract and emphasized the importance of examination of the vagina no matter whether CIN is suspected.

VaIN can be relatively more challenging after hysterectomy, especially when medical and conservative options have failed. In our study, 81 of the 657 patients underwent total hysterectomy. Among these patients, 66.7% underwent this operation due to cervical factors indicating cervical cancer or precancer. The proportion of patients with VaIN 2/3 was higher among those who underwent hysterectomy than among the patients who had not undergone hysterectomy, suggesting that the severity of VaIN was associated with hysterectomy. Similarly, Cao *et al.* [3] reported the incidence of VaIN was higher in patients who had undergone hysterectomy due to cervical factors. The reason may be associated with that many women receiving hysterectomy because of high-grade CIN or cervical cancer. The latest literature reports that the incidence of postoperative vaginal cancer in patients undergoing total hysterectomy with prevalent CIN is significantly increased and that the increased risk lasts for more than 10 years [2]. Patients with VAIN after hysterectomy attend multiple hospital visits, which is burdensome and increases healthcare service costs. Therefore, we suggest the entire vagina should be routinely inspected by colposcopy prior to hysterectomy to ensure that VaIN is identified. If it is diagnosed during the definitive management of CIN at the time of hysterectomy and is confined to the upper vagina, it could be surgically treated at the same time.

There is no clear consensus on the effectiveness of different tests for VaIN. In our study, the sensitivity of cytology for VaIN after hysterectomy was higher than the sensitivity of cytology for VaIN without hysterectomy for both VaIN 2/3 and VaIN 1. In patients without hysterectomy, the sensitivity of cytology was higher for those with concomitant VaIN than those with only VaIN. The sensitivity of TCT for the diagnosis of VAIN was not high because the main sampling site for TCT was not squamous epithelial cells of the vaginal wall. In patients with a high suspicion of VAIN, sampling site selection may increase the sensitivity of screening.

In our study, in patients who did not undergo hysterectomy, the sensitivity of hrHPV for VaIN 2/3 and VaIN 1 was 89.3% and 86.8%, respectively. The sensitivity of hrHPV for VaIN 2/3 and VaIN 1 after hysterectomy was 93.3% and 62.5%, respectively. In our study, hrHPV sampling of VaIN 1 in patients

TABLE 4. Cytology/hrHPV cotesting reports for 657 patients with VaIN.

VaIN	N	cytology sensitivity	hrHPV sensitivity	cotesting sensitivity
No hysterectomy	576	60.00%	87.40%	95.00%
VaIN 2/3	142	68.30%	89.30%	96.50%
VaIN 1	434	56.70%	86.80%	94.90%
Only vaginal lesions	418	56.70%	87.70%	95.20%
VaIN 2/3	100	65.00%	90.80%	97.00%
VaIN 1	318	54.40%	86.80%	94.70%
Concomitant lesions	158	66.50%	86.50%	95.60%
VaIN 2/3	42	76.20%	85.40%	95.20%
VaIN 1	116	62.90%	87.00%	95.70%
After hysterectomy	81	72.30%	74.30%	95.00%
VaIN 2/3	32	80.00%	93.30%	97.00%
VaIN 1	49	67.40%	62.50%	93.80%

VaIN: vaginal intraepithelial neoplasia; hrHPV: high-risk human papillomavirus.

TABLE 5. hrHPV reports of 657 patients with VaIN.

Vaginal intraepithelial neoplasia	Total	16+	18+	HPV others+ (non 16/18)	negative
No hysterectomy	576	72	6	332	72
VaIN 2/3	142	31	2	61	15
VaIN 1	434	41	4	271	57
Only vaginal lesions	417	44	4	251	51
VaIN 2/3	99	18	1	48	9
VaIN 1	318	26	3	203	42
Concomitant lesions	158	28	2	80	21
VaIN 2/3	42	13	1	12	6
VaIN 1	116	15	1	68	15
After hysterectomy	81	19	3	30	20
VaIN 2/3	32	18	2	4	2
VaIN 1	49	1	1	26	18

VaIN: vaginal intraepithelial neoplasia; hrHPV: high-risk human papillomavirus; 16+: positive for HPV-16; 18+: positive for HPV-18; HPV others+ (non 16/18): positive for the other 12 types other than 16/18.

after hysterectomy was low, the VaIN 1 diagnosis is poorly reproducible with false positive and false negative diagnoses, especially when the pathologist cannot use immunostaining with p16 to confirm the diagnosis (as in VaIN 2/3). Cytology and hrHPV cotesting increased the sensitivity of hrHPV testing for VaIN 2/3 and VaIN 1 in patients who did not undergo hysterectomy (96.5% and 94.9%, respectively). The sensitivity of cytology and hrHPV contesting for VaIN 2/3 and VaIN 1 after hysterectomy was 97% and 93.8%, respectively. This finding is consistent with that of a British study, which showed that in more than half of the patients, regardless of the VaIN grade, a combination of cytology and colposcopy was used for follow-up [9].

Previous studies have shown that HPV 16 is the main virus type associated with the development of VaIN [12]. In L. Alemany's research, the largest VaIN 2/3 dataset published until 2014, they described the HPV DNA prevalence and type distribution in a large series of 189 VaIN 2/3 patients from 31 countries [13]. They found that the HPV prevalence in VaIN 2/3 lesions was 96%. The most common HPV type was HPV16, which was detected in 59% of VaIN 2/3 lesions among the HPV DNA-positive cases. Among VaIN 2/3 patients, the prevalence of HPV16 was followed by that of HPV18 (6%), HPV52 (6%), and HPV73 (5%). Other HPV types accounted for less than 5% each.

In our study, HPV genotyping was significantly different in patients with VaIN 1 and VaIN 2/3. In patients with VaIN 1, the other 12 hrHPV subtypes indicated an incidence as high as 73.2%. However, in patients with VaIN 2/3, HPV16 and/or HPV18 was the main virus type, accounting for 57.5%. This finding suggests that the severity of VaIN was associated with HPV genotyping. In clinical practice, we should also pay more attention to patients who are infected with the other 12 hrHPV subtypes.

5. Conclusions

In summary, a combination of cytology and hrHPV testing increased the sensitivity of the diagnosis of VaIN. The severity of VaIN was associated with HPV genotyping and hysterectomy, but not with concomitant cervical or vulvar lesions. HPV 16 and 18 are the most frequent subtypes in VaIN 2/3. The other 12 hrHPV subtypes were the main virus types associated with the development of VaIN 1.

AUTHOR CONTRIBUTIONS

MF and WY—designed the research study. MF—performed the research. MF and CY—analyzed the data and wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Institutional Review Board (IRB) of the International Peace Maternal and Child Health Hospital approved this retrospective study (No. 20200606L).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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