A Retrospective Study of 657 Women With Vaginal Intraepithelial Neoplasia (VaIN)

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Research Article

Keywords: VaIN, HPV, Cytology test, Hysterectomy

Posted Date: November 11th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-655431/v1

Abstract

Objective: The aim of this study was to explore the clinical characteristics of patients with VaIN and identify more sensitive diagnostic methods.

Methods: This study retrospectively analyzed 657 patients with VaIN from the International Peace Maternal and Child Health Hospital in Shanghai during a ten-year period.

Results: 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 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 hrHPV 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 who did not undergo hysterectomy, HPV16 was detected in 9.5% of VaIN 1 lesions among the HPV DNA-positive patients, while the other 12 types of HPV were detected in 62.6% of VaIN 1 lesions. In patients who underwent hysterectomy, HPV16 was detected in 2.1% of VaIN 1 lesions, and the other 12 types of HPV were detected in 54.2% of VaIN 1 lesions.

Conclusions: A combination of cytology and colposcopy could increase the sensitivity of the diagnosis of VaIN. The other 12 high-risk types of HPV positive may be more closely related to VAIN 1, more attention should be paid.

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 high-risk human papilloma virus (hrHPV) infections. Hysterectomized women have a more than doubled risk of contracting vaginal cancer compared with the risk among non-hysterectomized women in the general population [2]. With the rate of hysterectomy increasing in recent years, an increasing amount of research has focused on the risks of vaginal cancer. Recent research has shown that hysterectomized women with prevalent cervical intraepithelial neoplasia (CIN) at the time of surgery have a high risk of subsequent vaginal cancer. This risk remains elevated for at least 15 years [2].

Vaginal intraepithelial neoplasia (VaIN) is a premalignant disease that may lead to vaginal cancer. Except for a small amount of patients report postcoital spotting or unusual vaginal discharge, most patients have no obvious symptoms. Similar to Cervical intraepithelial lesion (CIN), there are three different subgroups of VaIN: low-grade squamous intraepithelial lesion (LSIL/ VAIN1) and high-grade squamous intraepithelial lesion (HSIL/ VAIN 2/3).

The early diagnosis of VaIN is important for the prevention of vaginal cancer, not only in women who with cervical precancerous lesions or cervical cancer but also in hysterectomized women with prevalent CIN at

the time of surgery.

VaIN was usually rarer because it was frequently underdiagnosed. In recent decades, with the development of screening methods, such as cytology, hrHPV test, and colposcopy in cervical cancer screening, the diagnosis of VaIN has increased steadily. It is important to improve the diagnostic rate of VaIN. However, owing to the rarity of vaginal HSILs, only 6 to 517 cases of VAIN have been reported in the current literature. Data on cytology, hrHPV, and colposcopy of VaIN are limited. Whether cytology is feasible as a VaIN screening method remains unknown. Few studies have focused on the role of HPV infection in vaginal HSILs; however, the HPV detection rate in VaIN lesions is controversial.Chao et al. reported that the HPV detection rate in VaIN was 69.3%[3], while other studies showed a higher detection rate of 90-100%[4][5].

In this study, we prospectively 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, cytology/hrHPV sensitivity, and previous hysterectomy indications among patients with VaIN.

Materials And Methods

We performed a retrospective study from January 1, 2009, until December 31, 2019. Data were collected from the electronic database of the International Peace Maternal and Child Health Hospital in Shanghai. 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 (USA). The Bethesda 3-tier system was used as the cervical cytological diagnostic criteria. Atypical squamous cells, not excluding high-grade squamous intraepithelial lesions (ASC-H), low-grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesions (HSIL), or squamous cell carcinoma (SCC), were regarded as abnormal TCT results. HPV status was determined by the Cobas 4800 Human Papillomavirus (HPV) Test. The test utilizes amplification of target DNA by the Polymerase Chain Reaction (PCR) and nucleic acid hybridization for the detection of 14 high-risk (HR) 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, Chicago, IL, USA). Differences were considered statistically significant if $P<.05$. Student’s t test and Fisher’s exact test were used to compare differences between outcomes.

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.

Table 1: Original composition of vaginal, cervical, and vulvar lesions

Vagina	Cervix	Vulva	Number
HSIL	/	/	132
HSIL	CA	/	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; / stands for no lesion.			

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% were diagnosed with only VaIN, and 27.4% were diagnosed with VaIN concomitant with cervical or vulvar lesions. Among patients with only VaIN, 23.9% were diagnosed with VaIN 2/3, and 76.1% were diagnosed with VaIN 1. Among those with concomitant VaIN, 26.6% were diagnosed with VaIN 2/3, and 73.4% were diagnosed with VaIN 1. The proportion of patients with VaIN 2/3 among patients with concomitant cervical lesions was similar to that among patients with only VaIN (p= 0.5169).

Among 81 patients with a history of hysterectomy, 39.5% were diagnosed with VaIN 2/3 and 60.5% with VaIN 1. The proportion of patients with VaIN 2/3 among patients who underwent hysterectomy (39.5%) was higher than that among patients who did not undergo hysterectomy (24.7%) (p = 0.0068). (Table.2)

Table 2: VaIN diagnosed after hysterectomy or with no hysterectomy

VaIN			N	Proportion
No hysterectomy			576	100%
	VaIN 2/3		142/576	24.70%
	VaIN 1		434/576	75.30%
	Only vaginal lesions lesions		418/576	72.600%
		VaIN 2/3	100/418	23.900%
		VaIN 1	318/418	76.100%
	Concomitant lesions		158/576	27.400%
		VaIN 2/3	42/158	26.600%
		VaIN 1	116/158	73.400%
After hysterectomy			81	100%
	VaIN 2/3		32/81	39.5%
	VaIN 1		49/81	60.5%

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 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%).

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

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

Table 4: Cytology reports of 657 cases of VaIN

VaIN		N	Cytology number							
			NILM	ASCUS	LSIL	ASC-H	HSIL	CA	missing	sensitivity
No hysterectomy		576	233	155	153	9	22	4		60%
	VaIN2/3	142	45	34	44	3	13	3		68.30%
	VaIN1	434	188	121	109	6	9	1		56.70%
	Only vaginal lesions	418	181							56.70%
	VaIN2/3	100	35	27	32	0	5	0		65.00%
	VaIN1	318	145	91	74	3	5	0		54.40%
	Concomitant lesions	158	53							66.50%
	VaIN2/3	42	10	7	12	3	8	3		76.20%
	VaIN1	116	43	30	35	3	4	1		62.90%
After		81	21	19	20	5	9	2		72.30%
	VaIN2/3	32	6	5	7	3	7	2	2	80%
	VaIN1	49	15	14	13	2	2	0	3	67.4

NILM: negative for intraepithelial lesion or malignancy; ASCUS: atypical squamous cells of undetermined significance; LSIL: low-grade squamous intraepithelial lesion; ASC-H: atypical squamous cells cannot exclude HSIL; HSIL: high-grade squamous intraepithelial lesion; CA: cancer.

The available hrHPV reports of 657 cases of VaIN were classified as shown in Table 5. Among 576 cases of VaIN without hysterectomy, the sensitivity of hrHPV was 89.30% for VaIN 2/3 and 86.8% for VaIN 1. Among 417 cases of only VaIN, the sensitivity of hrHPV was 87.7%, and the sensitivity of hrHPV for VaIN 2/3 was 90.8%. Among 158 cases of concomitant VaIN, the sensitivity of hrHPV was 85.40% for VaIN 2/3 and 87.0% for VaIN 1. For VaIN concomitant with cervical cancer, HSIL, LSIL, and hrHPV, the sensitivity is above 83.30%. Among 81 cases of VaIN after hysterectomy, for VaIN 2/3, the sensitivity of hrHPV was 93.3%; however, the sensitivity for VaIN 1 was only 62.50%.

Table 5: hrHPV reports of 657 cases of VaIN

VaIN		Total	16+	18+	other 12 types+	both/all+	negative	missing	sensitivity
No hysterectomy		576	72	6	332	91	72	3	87.40%
	VaIN 2/3	142	31	2	61	31	15	2	89.30%
	VaIN 1	434	41	4	271	60	57	1	86.80%
Only vaginal lesions		417	44	4	251	66	51	1	87.70%
	VaIN 2/3	99	18	1	48	22	9	1	90.80%
	VaIN 1	318	26	3	203	44	42	0	86.80%
Concomitant lesions		158	28	2	80	25	21	2	86.50%
	VaIN 2/3	42	13	1	12	9	6	1	85.40%
	VaIN 1	116	15	1	68	16	15	1	87.00%
After hysterectomy		81	19	3	30	6	20	3	74.30%
	VaIN 2/3	32	18	2	4	4	2	2	93.30%
	VaIN 1	49	1	1	26	2	18	1	62.50%

16+: Positive for HPV-16; 18+: Positive for HPV-18; other 12 types+: Positive for the other 12 types; both/all: Positive for two of HPV16, HPV18, the other 12 types/positive for all types of HPV.

Cytology/hrHPV cotest reports were available for 657 patients with VaIN (Table 6). Cotest 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 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 was 95.0%, 93.8%, and 97.0%, respectively.

Table 6: Cytology/hrHPV cotest reports of 657 cases of VaIN

VaIN			cytology sensitivity	hrHPV sensitivity	Cotest sensitivity
No hysterectomy			60%		95%
		VaIN 2/3	68.30%	89.30%	96.50%
		VaIN 1	56.70%	86.80%	94.90%
	Only vaginal lesions		56.70%		95.20%
		VaIN 2/3	65.00%	90.80%	97.00%
		VaIN 1	54.40%	86.80%	94.70%
	Concomitant lesions		66.50%		95.60%
		VaIN 2/3	76.20%	85.40%	95.20%
		VaIN 1	62.90%	87.00%	95.70%
After hysterectomy			72.30%		95%
		VaIN 2/3	80%	93.30%	97%
		VaIN 1	67.4%	62.50%	93.80%

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 [6], and as the HPV infection rate increased, cervical fluid-based cytology improved, and HPV detection and colposcopy increased, the incidence of VaIN increased. VAIN is classified into low-grade VAIN (VAIN 1) and high-grade VAIN (including VAIN 2 and VAIN 3) based on the depth of the involved epithelium. 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%[7]. 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[8]. In the Dodge study, 65% of cases of VaIN coexisted with CIN, but there are also many literature reports in which the proportion of independent VaIN is also large[9]. The study of Sui et al reported that the proportion of VaIN patients with combined CIN ranges from 29.58–33.83%[7]. Similarly in our study, among 576 patients without a history of hysterectomy, 72.6% were diagnosed with only VaIN, and 27.4% were diagnosed with VaIN concomitant with cervical or vulvar lesions. The proportion of patients with VaIN 2/3 among patients with concomitant cervical lesions was similar to that among patients with only VaIN (p= 0.5169).

Similar to CIN, there are three different grades of VaIN. VaIN 1 is also known as a low-grade squamous intraepithelial lesion (LSIL), whereas VaIN 2 and VaIN 3 are both high-grade squamous intraepithelial lesions (HSILs). Studies have shown that the proportion of patients with VaIN 2/3 is higher among patients who have undergone hysterectomy than in patients who have not undergone hysterectomy[10].

Our results are consistent with those of previous studies (hysterectomy group 39.5% vs. no hysterectomy group 24.7%). Sui et al. retrospectively analyzed 529 patients with VaIN, and 17.8% of the patients had a history of hysterectomy[7]; 83.9% of these patients were diagnosed with VaIN 1, and 16.1% were diagnosed with VaIN 2/3. In our study, 657 patients with VaIN were included, and 12.3% had a history of hysterectomy, including 60.5% of patients with VaIN 1 and 39.5% of patients with VaIN 2/3. The proportion of posthysterectomy patients in a previous study was higher than that in our study, while the proportion of patients with VaIN 2/3 in our study was higher than that in a previous study. In our institution, the proportion of patients with VaIN 2/3, regardless of whether hysterectomy had been performed, was higher than the proportions reported elsewhere, which is a cause for concern.

VaIN can be relatively more challenging after hysterectomy, especially when medical and conservative options have failed. The incidence of VaIN was higher in patients who had undergone hysterectomy due to cervical factors. 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 (48.1%) or precancer (51.9%). A total of 33.3% underwent hysterectomy for noncervical lesions. In the study by Zhang, among the 99 patients with stage I cervical cancer or CIN III combined with VaIN undergoing hysterectomy, 12 patients (including 11 patients within 3 years after surgery) were followed up for 1-5 years and exhibited residual VaIN. Among the 12 patients with residual VaIN, 11 did not receive vaginal wall biopsy under colposcopy before surgery; among these patients, 4 with residual VaIN progressed, 2 patients developed vaginal cancer, and the residual recurrence rate was 2%. In addition, patients undergoing hysterectomy due to noncervical factors are not routinely followed up, but 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[11]. Patients with VAIN after hysterectomy attend multiple hospital visits, which is burdensome and increases healthcare service costs. Therefore, 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 concomitant VaIN than for only VaIN.

HPV testing is still controversial in the context of the diagnosis of VaIN. Some literature reports show that the HPV positive rate is low. Lamos et al. reported that the HPV positive rate was 66.7% among 9 cases of VaIN 1 and 66.7% among 58 cases of VaIN 2/3 [12]. Wee et al. found that the HPV positive rate among 21 VaIN patients was 66.9%[13]. Some of the literature has reported higher HPV positive rates. So et al. found that the detection rates of HPV in VaIN 1, VaIN 2 and VaIN 3 patients were 74.3%, 85.7% and 100%, respectively[14]. In the study of Sui et al., the HPV positive rate among VaIN patients was 87.82%, among which the HPV positive rates of VaIN 1 alone, VaIN 2/3 alone, VaIN 1 after hysterectomy, and VaIN 2/3

after hysterectomy were 84.46%, 88.71%, 85.03%, and 91.36%, respectively[7]. 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 after hysterectomy was low, possibly due to incomplete sampling in women after hysterectomy.

Cytology and hrHPV cotesting increased the sensitivity of hrHPV 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 cotesting 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 the patients, regardless of the VaIN grade, a combination of cytology and colposcopy was used for follow-up [8].

Previous studies have shown that HPV 16 is the main virus type associated with the development of VaIN [15]. Interestingly, HPV types differ between low-grade and high-grade vaginal dysplasia. 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[16]. 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, in patients without hysterectomy, HPV16 was detected in 22.10% of VaIN 2/3 lesions among the HPV DNA-positive cases, and the other 12 types were detected in 43.6% of VaIN 2/3 lesions. In patients who underwent hysterectomy, HPV16 was detected in 60.00% of VaIN 2/3 lesions among the HPV DNA-positive cases, and the other 12 types were detected in 13.3% of VaIN 2/3 lesions. In patients without hysterectomy, HPV16 was detected in 9.5% of VaIN 1 lesions among the HPV DNA-positive cases, and the other 12 types were detected in 62.6% of VaIN 1 lesions. In patients who underwent hysterectomy, HPV16 was detected in 2.1% of VaIN 1 lesions among the HPV DNA-positive cases, and the other 12 types were detected in 54.2% of VaIN 1 lesions. In our study, HPV16 account for a large proportion among patients with VaIN 2/3, especially among patients who underwent hysterectomy, but for VAIN 1, the 12 other types of high-risk HPV infections are more closely related compared with HPV16. This finding suggests that in clinical practice, we should also pay more attention to patients who are positive for the 12 types of high-risk HPV, and inspection of the entire vagina by colposcopy is recommended.

Declarations

Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Ethic Committee (EC) from the International Peace Maternity and Child Health Hospital, School of Medicine, Shanghai Jiao Tong University.

Authors' contributions

Dr. Meng: Data Collection, Data analysis, Manuscript writing

Dr. Cao: Data Collection, Manuscript writing

Dr. Wang: Project development, Manuscript revision

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