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Clinical analysis of cervical intraepithelial neoplasia with vaginal intraepithelial neoplasia

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Abstract

The purpose of this prospective cohort study is to evaluate the importance of screening and its diagnostic accuracy compared with the pathological diagnosis of cervical intraepithelial neoplasia (CIN) with vaginal intraepithelial neoplasia (VAIN).

The prospective study enrolled 419 patients (pts) and was conducted between February 1, 2015 and January 31, 2016 at Beijing Obstetrics and Gynecology Hospital, Capital Medical University.

All enrolled pts underwent multipoint biopsy of cervix and vaginal wall directed by colposcopy. All samples of biopsy underwent pathological examination. Among them, 201 pts (48.0%) were diagnosed with CIN, 218 pts (52.0%) were diagnosed with cervicitis, and 51 pts (12.2%) were diagnosed with VAIN. It was found that the incidence of CIN in pts was 4 times higher than that of VAIN. In all 419 patients enrolled, 218 pts had cervicitis with 13 pts (6.0%) of VAIN. There were 201 pts of CIN with 38 pts (18.9%) of VAIN: including 53 pts of CIN3 with 12 pts (22.6%) of VAIN; 49 pts of CIN2 with 9 pts of VAIN (18.4%), and 99 pts of CIN1 with 17 pts of VAIN (17.2%). The incidence of CIN with VAIN (18.9%) was significantly higher than cervicitis with VAIN (6.0%) ($\chi^2 = 16.39$, $P = .00$). Our results showed that there was a significant consistency between cervical lesions and vaginal lesions ($\chi^2 = 135.91$, $P = .00$), which indicated that the increase of CIN grades may be related to an increase of the VAIN grades. Our results also showed the significant ($p < .05$) increase of CIN and VAIN with age (<40 years Kappa = 0.04; 40–50 years Kappa = 0.11; >50 years Kappa = 0.28).

This study showed that cytological test can be used as a routine screening method for cervical lesions and vaginal diseases. If the cytology result shows abnormality, and pathological examination confirms that there is no obvious abnormal cervical disease, colposcopy directed vaginal multipoint biopsy should be conducted to exclude vaginal disease. All patients of CIN should routinely undergo vaginal multipoint biopsy (1/3 upper vagina), especially in patients with high-grade CIN and age older than 50 years.

Abbreviations: ASCUS = atypical squamous cells of undetermined significance, CIN = cervical intraepithelial neoplasia, HPV = human papilloma virus, HSIL = high-grade squamous intraepithelial lesion, LSIL = low-grade squamous intraepithelial lesion, NILM = negative for intraepithelial lesion or malignancy, SCC = squamous cell carcinoma, VAIN = vaginal intraepithelial neoplasia.

Keywords: cervical intraepithelial neoplasia, precancer prevention, screening, sensitivity and specificity, vaginal intraepithelial neoplasia

1. Introduction

In recent years, more and more young women were diagnosed with cervical cancer. The statistics showed that among all cervical cancer patient the percentages of young (under age of 35 years old) patients rose from 3.4% in 1960 to 24.9% in 2005.[1] High-grade cervical intraepithelial neoplasia (CIN2–3) is the precancerous lesion of cervical cancer. Along with the progress in screening cervical cancer; many patients with cervical precancerous lesions were found and treated in time with good prognosis. Vaginal intraepithelial neoplasia (VAIN) is a rare human papilloma virus (HPV)-related premalignant condition that can be histologically diagnosed and characterized by dysplastic changes in the vaginal epithelium without stromal invasion.[2] It accounts for about only 0.4% of female lower genital tract intraepithelial lesions, with an incidence from 0.2 to 2 per 100,000 women per year.[3] Persistent high-risk HPV infection is considered a necessary condition to develop VAIN. Our previous study[4] showed that 15% of patients with VAIN after hysterectomy due to stage I cervical cancer and CIN3, all of the VAIN lesions occurred in the 1/3 upper vagina. Among them, 4% of vaginal lesions will progress and 2% will develop into vaginal stump cancer that is very difficult to treat. Because insufficient preoperative assessment often leads to insufficient vaginal resection and results in vaginal lesions residues to cause stump VAIN, we recommend that CIN and early cervical cancer patients should undergo routine colposcopy vaginal wall biopsy to determine the scope of hysterectomy.

At present, there have been reports supporting that CIN is a high risk factors of VAIN for patients who underwent hysterectomy. With cervical lesion, the rate of VAIN progressing to vaginal cancer is about 5.8%.[3,5,6] There are not many prospective studies of cervical lesions with VAIN due to the fact

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that the incidence of stump VAIN rate increasing gradually and the treatment is very difficult. Now more and more gynecologic oncologists are paying attention to the diagnosis of CIN with VAIN. Whether cytology is feasible as a VAIN screening method and whether there is a consistency between CIN and VAIN occurrence remains a question.

In this study, we prospectively recruited 419 patients who underwent colposcopy directed cervical and vaginal biopsy at the same time. The objective of this study is to provide some clinical evidence to standardized the screening and estimate its diagnostic accuracy of CIN with VAIN.

2. Methods

2.1. Study participants

A prospective cohort study of diagnosis test was designed and approved by the Ethic Committee (EC) from the Beijing Obstetrics and Gynecology Hospital. The study was conducted in the hospital from February 1, 2015 to January 31, 2016. A total of 419 patients with the following inclusion/exclusion criteria and signed the informed consent were enrolled.*Inclusion criteria*: Abnormal cytological results according to the Bethesda system.[7] If the cytology results showed abnormal, the cervical and vaginal biopsies were then performed. Patients with normal cytology results but with HR-HPV persistent infections more than 1 year were categorized as a high-risk group for further cervical and vaginal biopsy under colposcopy to confirm the diagnosis. The pts in this group were also approached and enrolled after signing the informed consent. *Exclusion criteria*: previous hysterectomy, gynecological malignant tumor, vaginal drug treatment, previous vaginal surgery, previous laser therapy and pts who refused cervical or vaginal biopsy.

2.2. Cytology screening (TCT screening)

All patients underwent a routine pathological examination. The TCT screening was carried out using a ThinPrep 2000 Processor (USA), an automated slide preparation unit that performs liquid-based cytology tests. Liquid-based specific cytology brushes were used for insertion into the cervical canal to collect epithelial cells which were sent to a cytological laboratory for inspection. The slides were examined by specialists with at least 10 years of experience. The Bethesda 3-tier system was used as the cervical cytological diagnostic criteria.[7] Atypical squamous cells—cannot exclude high-grade squamous intraepithelial lesion (ASC-H), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), and squamous cell carcinoma (SCC) were regarded as abnormal TCT results, colposcopy directed cervical, and vaginal biopsy were performed. Patients with atypical squamous cells of undetermined significance (ASCUS) underwent HR-HPV test or a second TCT test, during which the colposcopy and biopsy were performed if they were tested HR-HPV positive or the second TCT confirmed ASCUS, ASC-H, LSIL, HSIL, or SCC with the consent of the patients.

2.3. HPV testing

A modified soft cone-shaped cervical brush (Cervical Sampler, Digene Corp., Gaithersburg, MD) was used to obtain samples from the cervix or vaginal vault for HPV testing by Hybrid Capture 2 (HC2, Digene Diagnostics, Gaithersburg, MD) or HR-HPV type test (Cervista, Hologic Diagnostics, Marlborough, MA). HC2 is an in vitro nucleic acid hybridization assay that can detect 13 high-risk types of HPV DNA (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68).

2.4. Colposocpy directed biopsy

Colposcopy was performed by 2 attending physicians using an EDNA C6 stereomicroscope (EDAN Instruments, Inc., Wuhan, China). Both physicians had at least 5 years of experience with colposcopy examination, performing 500 procedures each year. A standard colposcopy protocol was adopted in the present study, including the acetic acid test and Lugol's iodine experiment.[8] The classification and initial diagnosis of abnormal colposcopy were described in the 2003 International Federation for Cervical Pathology and Colposcopy (IFCPC) terminology.[9]

Cervical and vaginal biopsies of the most suspicious lesion under colposcopy were analyzed by 2 consultant pathologists (cervix in 4 sections, vagina in 1–2 sections), and 5% of the total number of slides were reviewed and double checked every 3 to 6 months. The WHO classification of tumors pathology and genetic tumors of the breast and female genital organs was used for pathological diagnosis.[8] The pathological diagnostic grade was based on the worst pathology results.

2.5. Statistical analysis

The SPSS package ver.20.0 (SPSS, Inc., Armonk, NY) was used to perform the statistical analysis. The categorical data were analyzed using the χ^2 test, the consistency detection was analyzed using McNemanr method and the Kappa statistics. The difference was considered statistically significant if $P < .05$.

3. Results

Figure 1 shows the flowchart of the study. Of the 419 pts underwent multipoint biopsy under the guidance of colposcopy, 201 pts (48.0%) were diagnosed with CIN, 218 pts (52.0%) were diagnosed with cervicitis. Fifty-one pts (12.2%) were diagnosed with VAIN, 368 pts (87.8%) were diagnosed with vaginitis. The incidence of CIN was 4 times higher than that of VAIN and no patient was found with cervicitis or CIN with vaginal invasive cancer.

3.1. Comparison of cytological screening results in different pathological diagnosis of cervix and vagina

A total of 419 pts underwent multipoint biopsy under the guidance of colposcopy and 201 pts (48.0%) had CIN based on the pathological diagnostic examination. Among them, 180 pts had abnormal cytology test (the detection rate of CIN screening by cytology was 89.6%); the remaining 21 pts with negative (or normal) cytology generated a rate of 10.4% CIN false negative for the cytology screening (see Table 1). The difference between the cytology screening and pathological diagnosis results of CIN were significant ($\chi^2 = 47.05$, $P = .00$). For the 51 pts (12.2%) with pathological diagnosis of VAIN, 46 pts (90.2%) were diagnosed with abnormal cytology test. The difference between the cytology screening and pathological diagnosis results of VAIN were significant ($\chi^2 = 55.36$, $P = .00$) (see Table 2). For the 218 pts with pathological diagnosis of cervicitis, 177 pts (81.2%) had abnormal cytology results, 41 pts (18.8%) had normal cytology results. No significant difference was found between the

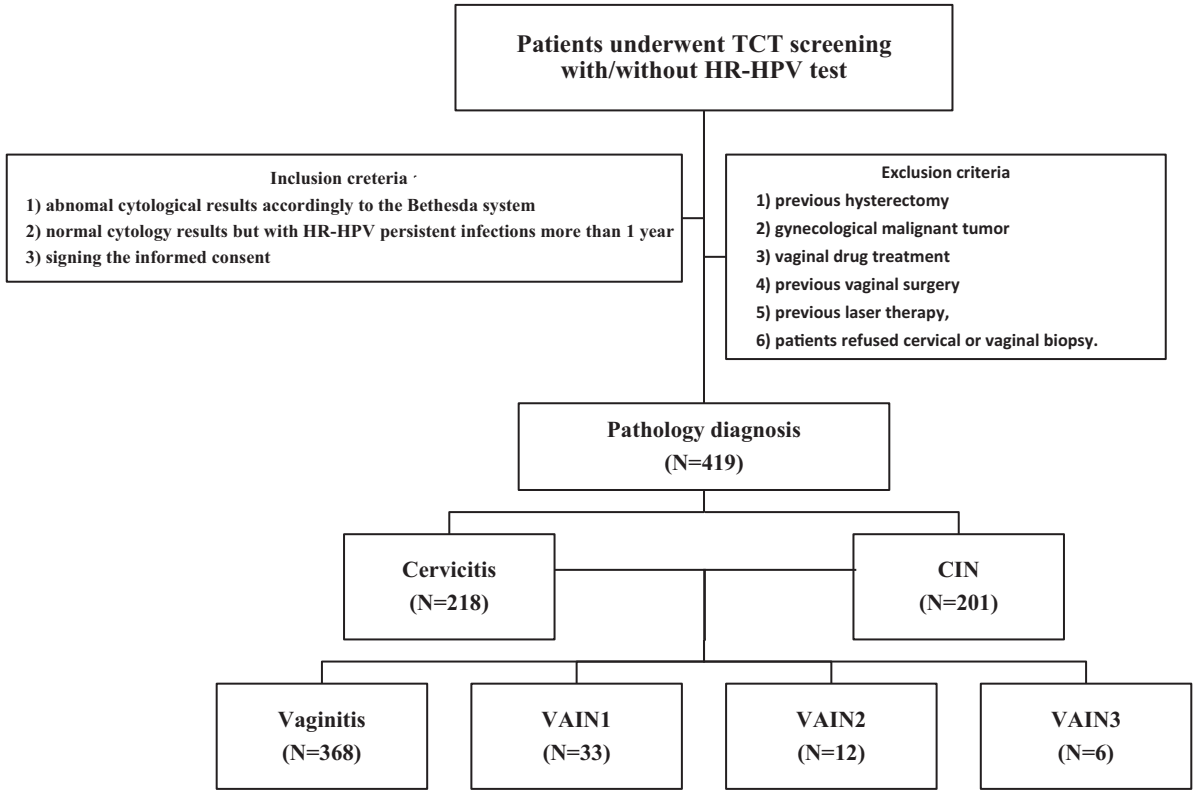

Figure 1. Study flowchart of the 419 pts underwent multipoint biopsy under the guidance of colposcopy according to the inclusion criteria and exclusion criteria after pts underwent TCT with/without HR-HPV, 201 pts (48.0%) were diagnosed with CIN, 218 pts (52.0%) were diagnosed with cervicitis. Fifty-one pts (12.2%) were diagnosed with VAIN (including 33 pts had VAIN1, 12 pts had VAIN2, 6 pts had VAIN3), 368 pts (87.8%) were diagnosed with vaginitis.

cytological and pathological results for VAIN in cervicitis ($\chi^2 = 10.55$, $P = .31$). For the 177 pts with abnormal cytology tests, 12 pts (6.8%) were diagnosed with VAIN. For the 41 pts with normal cytology test, 1 pt (2.4%) was diagnosed with VAIN (see Table 3).

3.2. Comparison of different grades of VAIN with different grades of CIN

Comparing the demographic information (age, child birth, status of chronic disease) of patients in different grades of CIN, it showed that the age is significant risk factor of CIN grade ($\chi^2 = 15.02$, $P = .02$) (see Table 4). Among the 218 pts diagnosed with cervicitis by pathological examination, 13 pts (6.0%) had VAIN, in which 3 pts had VAIN2–3 and 10 pts had VAIN1. For the 201 pts diagnosed with CIN by pathological examination, 38 pts (18.9%) had VAIN: Among the 53 pts diagnosed with CIN3, 12 pts (22.6%) had VAIN, in which 7 pts had VAIN2–3 and 5 pts had VAIN1; in 49 patients diagnosed with CIN2, 9 pts (18.4%) had VAIN, of which 3 pts had VAIN2–3 and 6 pts had VAIN1; in 99 patients diagnosed with CIN1, 17 pts (17.2%) had VAIN, of which 5 pts were VAIN2–3 and 12 pts were VAIN1. With the increase of CIN grades, the incidences of VAIN increased, the incidence of CIN with VAIN (18.9%) was significantly higher than that of cervicitis with VAIN (6.0%) ($\chi^2 = 16.39$, $P = .00$). There was a consistency between cervical lesions and vaginal lesions ($\chi^2 = 135.91$, $P = .00$), with the increase of CIN grades, there was also an increase of the VAIN grades. When pts were

Table 1

Comparison of cytological screening results in different pathological diagnosis of cervix.

TCT	Cervix						
	Cervicitis	CIN1	CIN2	CIN3	Total	χ^2	*P*
NILM	41 (18.7%)	10 (10.1%)	7 (14.3%)	4 (7.6%)	62		
ASC	75 (34.4%)	30 (30.3%)	12 (24.5%)	11 (20.8%)	128		
LSIL	88 (40.4%)	48 (48.5%)	17 (34.7%)	19 (35.8%)	172	47.05	.00
HSIL	13 (6.0%)	10 (10.1%)	12 (24.5%)	16 (30.1%)	51		
SCC	1 (0.5%)	1 (1.0%)	1 (2.0%)	3 (5.7%)	6		
Total	218	99	49	53	419		

The results were showed with n (%).

ASC = atypical squamous cells of undetermined significance (including ASCUS = atypical squamous cells of undetermined significance and ASC-H = atypical squamous cells—cannot exclude high-grade squamous intraepithelial lesion), CIN = cervical intraepithelial neoplasia, HSIL = high-grade squamous intraepithelial lesion, LSIL = low-grade squamous intraepithelial lesion, NILM = negative for intraepithelial lesion or malignancy, SCC = squamous cell carcinoma.

Table 2

Comparison of cytological screening results in different pathological diagnosis of vagina.

TCT	Vagina						
	Vaginitis	VAIN1	VAIN2	VAIN3	Total	χ^2	*P*
NILM	57 (15.5%)	4 (12.1%)	0 (0.0%)	1 (16.7%)	62		
ASC	117 (31.7%)	9 (27.3%)	2 (16.7%)	0 (0.0%)	128		
LSIL	147 (40.0%)	16 (48.5%)	8 (66.6%)	1 (16.7%)	172	55.36	.00
HSIL	44 (12.0%)	3 (9.1%)	2 (16.7%)	2 (33.3%)	51		
SCC	3 (0.8%)	1 (3.0%)	0 (0.00%)	2 (33.3%)	6		
Total	368	33	12	6	419		

The results were showed with n (%).

ASC = atypical squamous cells of undetermined significance (including ASCUS = atypical squamous cells of undetermined significance and ASC-H = atypical squamous cells—cannot exclude high-grade squamous intraepithelial lesion), HSIL = high-grade squamous intraepithelial lesion, LSIL = low-grade squamous intraepithelial lesion, NILM = negative for intraepithelial lesion or malignancy, SCC = squamous cell carcinoma, VAIN = vaginal intraepithelial neoplasia.

Table 3

Cytological analysis of cervicitis with different grades of VAIN.

TCT	Cervix						
	Vaginitis	VAIN1	VAIN2	VAIN3	Total	χ^2	*P*
NILM	40 (19.5%)	0 (0.0%)	0 (0.0%)	1 (100%)	41		
ASC	72 (35.1%)	3 (30.0%)	0 (0.0%)	0 (0.0%)	75		
LSIL	80 (39.0%)	6 (60.0%)	2 (100%)	0 (0.0%)	88	10.55	.31
HSIL	13 (6.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13		
SCC	0 (0.00%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	1		
Total	205	10	2	1	218		

The results were showed with n (%). The incidence of CIN with VAIN 18.9% (38/201) was significantly higher than cervicitis with VAIN 6.0% (13/218) ($\chi^2 = 16.39$, $P = .00$).

ASC = atypical squamous cells of undetermined significance (including ASCUS = atypical squamous cells of undetermined significance and ASC-H = atypical squamous cells—cannot exclude high-grade squamous intraepithelial lesion), HSIL = high-grade squamous intraepithelial lesion, LSIL = low-grade squamous intraepithelial lesion, NILM = negative for intraepithelial lesion or malignancy, SCC = squamous cell carcinoma, VAIN = vaginal intraepithelial neoplasia.

divided into 3 age groups (younger than 40 years of old, 40–50 years of old and older than 50 years) the results further indicated that the consistency between CIN and VAIN were increasing with the increase of age (<40 years Kappa = 0.04; 40–50 years Kappa = 0.11; >50 years Kappa = 0.28), and all differences were statistically significant ($P < .05$) (see Table 5).

4. Discussion

4.1. The feasibility analysis of cytology test in CIN with VAIN

VAIN is a very rare and asymptomatic premalignant condition. It can be diagnosed through colposcopy-guided biopsy after an abnormal cytology test. According to the depth of the tissue involved, VAIN is generally classified as low-grade (mild dysplasia, VAIN1) or high-grade lesions (high-grade vaginal intraepithelial neoplasia [HG-VAIN]: VAIN2 and VAIN3, corresponding to moderate and severe dysplasia). Although the true prevalence of this condition is unknown in the past few decades, postmenopausal status and previous HPV-related cervical invasive or preinvasive lesions are well-known risk factors for the development of VAIN.[10] In the last 10 years, the incidence of VAIN has increased because of the widespread use of routine screening cytology tests.[8]

The correlation between abnormal cytology screening results and CIN has been investigated to a certain extent. But extensive

Table 4

General conditions of patients with CIN.

Vagina	Cervix					
	Cervicitis	CIN1	CIN2	CIN3	χ^2	*P*
Age, y						
<40	86 (39.5%)	53 (53.5%)	17 (34.7%)	28 (52.8%)	15.02	.02
40–50	70 (32.1%)	31 (31.4%)	22 (44.9%)	11 (20.8%)		
>50	62 (28.4%)	15 (15.1%)	10 (20.4%)	14 (26.4%)		
Child birth						
Yes	205 (94.0%)	86 (86.9%)	44 (89.8%)	48 (90.6%)	4.23	.19
No	13 (6.0%)	13 (13.1%)	5 (10.2%)	5 (9.4%)		
Chronic disease						
Yes	23 (10.6%)	9 (9.1%)	6 (12.2%)	10 (18.9%)	3.62	.31
No	195 (89.4%)	90 (90.9%)	43 (87.8%)	43 (81.1%)		
Total (419)	218	99	49	53		

The results were showed with n (%).

CIN = cervical intraepithelial neoplasia, VAIN = vaginal intraepithelial neoplasia.

Table 5

Comparison of different grades of VAIN with different grades CIN.

Age group, y	Vagina	Cervix					Kappa	χ^2	*P*
		Cervicitis	CIN1	CIN2	CIN3	Total			
<40	Vaginitis	80 (93.0%)	49 (92.5%)	15 (88.2%)	23 (82.1%)	167	0.04	73.62	.00
	VAIN1	4 (4.8%)	3 (5.7%)	1 (5.9%)	2 (7.1%)	10			
	VAIN2	1 (1.1%)	1 (1.8%)	1 (5.9%)	1 (3.7%)	4			
	VAIN3	1 (1.1%)	0 (0.0%)	0 (0.0%)	2 (7.1%)	3			
	Total	86	53	17	28	184			
40–50	Vaginitis	68 (97.1%)	25 (80.6%)	20 (91.0%)	10 (90.9%)	123	0.11	49.93	.00
	VAIN1	2 (2.9%)	4 (12.9%)	1 (4.5%)	0 (0.0%)	7			
	VAIN2	0 (0.0%)	2 (6.5%)	1 (4.5%)	0 (0.0%)	3			
	VAIN3	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)	1			
	Total	70	31	22	11	134			
>50	Vaginitis	57 (91.9%)	8 (53.4%)	5 (50.0%)	8 (57.2%)	78	0.28	16.67	.01
	VAIN1	4 (6.5%)	5 (33.3%)	4 (40.0%)	3 (21.4%)	16			
	VAIN2	1 (1.6%)	2 (13.3%)	1 (10.0%)	1 (7.1%)	5			
	VAIN3	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (14.3)	2			
	Total	62	15	10	14	101			
Total	Vaginitis	205 (94.0%)	82 (82.8%)	40 (81.6%)	41 (77.4%)	368	0.11	135.91	.00
	VAIN1	10 (4.6%)	12 (12.1%)	6 (12.2%)	5 (9.4%)	33			
	VAIN2	2 (0.9%)	5 (5.1%)	3 (6.2%)	2 (3.8%)	12			
	VAIN3	1 (0.5%)	0 (0.0%)	0 (0.0%)	5 (9.4%)	6			
	Total	218	99	49	53	419			

The results were showed with n (%).

CIN = cervical intraepithelial neoplasia, VAIN = vaginal intraepithelial neoplasia.

data on cytological abnormalities leading to the diagnosis of VAIN are lacking. One study analyzed the correlation between VAIN and the corresponding cytological abnormalities in the cytology test. It showed that 89% of women diagnosed with HG-VAIN had high-grade cytology.[5] Other reports suggested that SCC, HSIL, and ASC-H were considered "major cytological abnormalities." ASCUS and LSIL were considered "lesser abnormalities." Considering all the pts diagnosed with HG-VAIN, the proportion of major abnormalities and lesser abnormalities on the referral cytology test were similar. The most frequent cytological abnormality on the referral cytology test was HSIL. In 44.8% of the cases, however, the diagnosis of HG-VAIN was preceded by lesser cytological abnormalities.[11] These data are interesting, especially when comparing to the correlation between the CIN and the corresponding previous abnormality of cytology test. It was found that a high-grade cervical dysplasia is often preceded by major cytological abnormalities in most cases.[12,13] This is probably because the cytology is mostly carried out on the surface of the cervix exfoliated cells examination and it is difficult to take the exfoliated cells of vaginal area and fornix that are concealed. Because the cervix, vagina, and fornix are all in the same environment, their cytology results could interfere with each other.

All 419 pts enrolled in the study underwent colposcopy directed cervical and vaginal biopsy, and were screened by cytology test (TCT). For the 201 pts diagnosed with CIN, 180 had abnormal cytology (detection rate was 89.6%). For the 51 pts diagnosed with VAIN, 46 pts (90.2%) had abnormal cytology. The difference between the cytological and pathological results of CIN and VAIN were significant ($P < .05$). Since the TCT is carried out on the surface of the cervix exfoliated cells, inflammation cell coverage may be the cause of the false-negative rate of cytology screening. Failure to take inadequate amount of lesion cells due to the lesions' depth perhaps is another reason for the false-negative rate of the cytology screening. As a cervical lesions screening, the false-positive rate of TCT may be associated with the severe inflammatory cell dropping disturbance recognition of tumor cells. Because the vaginal lesions and the cervical lesions are in the same environment, with common etiology, the related vaginal lesions should also be considered.

It is further found that among the 13 pts pathologically diagnosed with cervicitis with VAIN, 12 of them had abnormal cytology. Only 1 cervicitis pt with VAIN3 had normal cytology. The detection rate of cytology screening for VAIN was 92.3%. The cytological grade and VAIN pathological grade were not entirely consistent.

It has been previously reported[11] that if cytology test is abnormal, it should be followed by a subsequent colposcopy with more accurate examination of the entire lower genital tract. An accurate examination of the whole vaginal walls and vault must be performed. Biopsy of all suspicious areas is mandatory, even when the cytological test before the colposcopy is less abnormal.

In summary, cytology test may be a good VAIN screening method. However, because the vaginal area is wide and the lesions are often located in the hidden places, cytology screening may have some false-negative results inconsistent with pathology examination. Because 6.0% of the patients with cervicitis may also have VAIN and 1.4% may also have HG-VAIN, even if the cytology screening of cervix is abnormal results and the colposcopy directed cervical biopsy is normal, more attention should still be paid to exclude vaginal lesions in order to avoid misdiagnosis.

4.2. The necessity of routine VAIN screening in patients with CIN

It has been reported that although the risk factors of VAIN and cervical intraepithelial neoplasia (CIN) are similar, the incidence of CIN is 100 times higher than that of VAIN.[14] This may be related to the lack of the vagina junction area in the vagina.[15] In addition, even if the HPV infection of the vagina is similar to that

of the cervix, the vaginal epithelial cell lysis may help the recovery of the lesion. In comparison with VAIN, cervical potential infection characteristics may lead to lesion continuity.[5,16] The results from this study of 419 pts showed that 201 pts were pathological diagnosed with CIN (incidence of CIN was 48.0%) and 51 pts were pathological diagnosed with VAIN (incidence of VAIN was 12.2%). So the incidence of CIN was 4 times higher than that of VAIN. Some study[5] reported lower incidence of VAIN (from 0.2 to 0.6 per 100,000 women per year). This may be due to the fact that the patients included in this study had abnormal cytology or persistent HR-HPV infections, rather than patients from the general population.

Our study also showed that the incidence of cervicitis with VAIN was 6.0% (13/218), CIN1 with VAIN was 17.2% (17/99), CIN2 with VAIN was 18.4% (9/49), CIN3 with VAIN was 22.6% (12/53). It is noticed that the incidence of CIN with VAIN (18.9%) was apparently higher than that of cervicitis with VAIN (6.0%). There was a consistency between the cervical lesions and the vaginal lesions with the increase of CIN grade, the grade of VAIN also increased (Kappa = 0.11, $P = .00$). But no patient with cervicitis or CIN in this study had vaginal cancer. The consistency between CIN and VAIN were increasing with age ($P < .05$). It was reported that etiological factors of VAIN and CIN may have a certain homological relationship.[17] Multiple risk factors (e.g., age, smoking, low social grade, multiple sexual partners, early sexual age, immunosuppression, reproductive tract disease history, etc.) of cervix, vulva, and anus intraepithelial neoplasia are also risk factors of VAIN. The risk factors mostly related to VAIN are CIN history and HPV infections. Another report[7] showed the incidence of VAIN after hysterectomy due to CIN is about 0.9% to 6.8%. For patient that had hysterectomy with high-grade CIN, the incidence of VAIN after hysterectomy may increase to 7.4%.

This study found that the incidence of CIN with VAIN was as high as 17.2% to 22.6%. There was a consistency between cervical lesion and vaginal lesion (when the CIN grade increases, the VAIN grade will also increase). The highest consistency was found in the group of patients that were 50 years or older. Based on the results of this study, we recommend that if a patient has a high CIN grade, more attention should be paid to the vaginal lesion at the time of cervical biopsy. In order to guide the treatment, routine vaginal biopsy is necessary to determine whether there are pathological changes and the grade of the VAIN lesion, especially for the for patient older than 50 years.

This study also showed that in CIN1 patients, 17.2% had VAIN, 5 CIN1 (5.1%) patients had HG-VAIN (VAIN2–3). Considering the development of CIN and VAIN are inconsistent, we also recommend routine colposcopy directed vaginal biopsy of suspicious places for patients with low grade of CIN (CIN1) to guide further treatment.

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