

Clinical significance of colposcopy on screening cervical intraepithelial neoplasia in cytological negative and smooth cervixes

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Abstract Objective: The aim of the study was to evaluate the clinical value of the video colposcopy in screening cervical intraepithelial neoplasia (CIN) in cytological negative and smooth cervixes by optically gynecological examination. **Methods:** The 1050 women, whose cervixes had been shown smooth and cytological negative by optical examine, were examined with electronic colposcopy in gynecological clinic, and biopsy was taken when the double abnormality of aceto-white epithelium and iodine negative, and other abnormal images were shown. A retrospective analysis of these cases was performed. **Results:** (1) The 514 samples from 458 cases, including 458 samples of abnormal tissues under colposcopy and 56 samples of polyp or polypoid tumors by optically, were examined by biopsy. Among them, 68 samples were found to be CIN, including 11 cases of CINII/CINIII; (2) The 72 of 1050 cases showed the double-abnormality of aceto-white epithelium and iodine negative. Among them, 64 cases were CIN determined by biopsy. And the positive predictive value of the double-abnormality of aceto-white epithelium and iodine negative under colposcopy was 88.9%, with a false negative rate of 3.3%; (3) Among 458 women examined by biopsy, only one of 350 samples from cervical polyp tissue was CIN (0.3%), while 67 of 164 samples from the tissues with abnormal colposcopic images were found to be CIN (40.9%), indicating the close relation between abnormal colposcopic findings and CIN; (4) The results of age-distribution analysis showed that, in the 164 cases with abnormal features under colposcopy, the incidence of double abnormality of aceto-white epithelium and iodine negative was higher in the age of sexual activity, just the same as the age distribution feature of CIN; while single abnormality of iodine negative appeared more in the age of over 50 years. **Conclusion:** Abnormal features displayed by colposcopy, especially the double abnormality of aceto-white epithelium and iodine negative, has an important significance for the screening of cervical precancerous lesions such as CIN. For this purpose, colposcopy examination is necessary even for the cases of cytological negative and smooth cervixes.

Key words precancerous lesion; cervical intraepithelial neoplasia (CIN); colposcopy; screen

Cervical intraepithelial neoplasia (CIN) is a premalignant condition of uterine cervix, and the histology grade II and III CIN (CINII and CINIII) are at high risk of progression to malignancy and may lead to the development of invasive cervical cancer. Screening for CIN and the early treatment, especially intervening high risk CINII/III and block the pathology process is very important for preventing the development of invasive cervical cancer.

Routine gynecological exam is very important in cervical cancer prevention. The usual recommendation of gynecological exam is to do routine gynecological exam, check the cervix optically, and run cervical cytology test at the same time. The colposcopy is only recommended when necessary, for example, there is abnormal cervical cytology result, suspicious lesions under optical cervix

exam or for clinical historical reason [1]. However, the screening for CIN at early stage with optimal exam is not efficient. Usually no histopathology test would be done for cytological negative and smooth cervix samples, while actually there might be abnormal cell proliferation [2]. Therefore there might be missing diagnosis for high risk CIN, or even precancerous cervical cancer. Since 1980s, many European countries have been including colposcopy as part of first routine gynecological exam, as well as histopathology test to increase screening rate for high risk CIN and precancerous cervical cancer [3]. To further evaluate the clinical value of the colposcopy in screening CIN, we collected and analyzed the samples from routine gynecological exam with cytological negative and smooth cervixes and reported as follows.

Materials and methods

General materials

We collected 1050 cases from the patients of gynecological clinic from May 2010 to September 2011 for routine gynecological exam and with the syndrome of gynecological disease except for cervicitis, vaginitis and pelvic inflammatory disease, and the cervixes showed smooth and cytological negative by optical examine. The patients aged from 22 to 64 years, with median of 43 years, and 998 patients (95.1%) had been given birth. The 951 cases were pre-menopausal and 99 were post-menopausal, and the median of menopausal age was 53 years. All the patients were excluded from virginal, cervixes, and acute vulva inflammation, as well as partial genital bleeding due to activity. Among all the cases, 528 (50.3%) of them had cervical hypertrophy, 761(72.5%) had Nessler cyst, and 350 (33.3%) had cervical polyps.

Colposcopy

As routine procedures. First, the full cervix was observed and images collected. Then visual inspection was executed with acetic acid test and iodine tests. The aceto-white epithelium was defined as positive and diagnosed as abnormality, indicating possible epithelial dysplasia. Normal cervix sample would show dark brown color for iodine test and it was defined as positive, indicating no suspicious pathological changes, while no dye was defined as negative, indicating immature metaplasia and atypical hyperplasia [3]. Biopsy was executed for the samples with cervical polyps and abnormal colposcopic images with the approval of patients after informing the test results and the importance of biopsy. The abnormal colposcopic images included double abnormality of aceto-white epithelium (positive result) and iodine negative, or solo abnormality of iodine negative, abnormal vein and abnormal glandular opening.

Cervical cell and histopathology test

Cervical cells were tested with thinprep cytological test (TCT), and histopathology was tested as routine procedure. All procedures executed by Clinical Pathology Laboratories of 81 Hospital of PLA, China.

Statistical method

Using chi-square test, with P -value < 0.05 as significant difference.

Results

The results of colposcopic acetic acid test and iodine test

We performed colposcopic acetic acid test and iodine test on all 1050 cases and found 72 (6.86%) cases with

Table 1 Biopsy results for 514 cervical pathological samples [n (%)]

Biopsy sample	n	CINI	CINII	CINIII	Total
Cervical polyps	350	1 (0.3)	0 (0)	0 (0)	1 (0.3)
Abnormal colposcopic images	164	56 (34.2)	8 (4.9)	3 (1.8)	67 (40.9)*

* $P < 0.05$

double abnormality (positive with acetic acid test and negative with iodine test), and 106 (10.10%) cases showed one abnormal test result, including 21 (2.0%) aceto-white epithelium (positive) and 85 (8.10%) iodine negative result.

The results of biopsy for screening CIN with colposcopy

Biopsy was taken for the patients with at least one of the following features: double abnormality of aceto-white epithelium and iodine negative, solo iodine negative, or cervical polyps. Totally 458 patients were examined by biopsy, among them 56 cases showed both abnormal colposcopic images and cervical polyps, thus provided samples from both suspicious position and polyps. The final sample number was 514. The 68 samples of CIN (14.9%) were diagnosed. Only one sample out of 68 was from cervical polyps and all other 67 samples were from samples with abnormal colposcopic images. The results was shown in Table 1.

Clinical importance of screening CIN by colposcopic acetic acid test and iodine tests

We analyzed 164 biopsy cases with abnormal colposcopic images and found 67 cases of CIN, including 11 cases of CINII/CINIII. Among them, 64 cases (95.5%) showed double abnormality of aceto-white epithelium and iodine negative, 2 cases (3.0%) showed only iodine negative, only 1 case showed abnormal glandular opening under colposcopy. The 64 out of 72 cases with double-abnormality of aceto-white epithelium and iodine negative were diagnosed as CIN by biopsy, which made the positive predictive rate of 88.9%. Only 3 out of 92 none double abnormality of aceto-white epithelium and iodine negative cases were diagnosed as CIN by biopsy, and this made the false negative rate of 3.3%.

Seven of these 164 cases showed abnormal glandular opening under colposcopy. Four out of those 7 cases were diagnosed as CIN and 3 of them showed double abnormality of aceto-white epithelium and iodine negative. The left 3 cases showed polypoid hyperplasia of the cervix, however no abnormality was observed for acetic acid and iodine tests, and no CIN was found under colposcopy.

Table 2 Age distribution for 164 samples of abnormal colposcopic acetic acid test and iodine test and CIN [n (%)]

Age (years)	n	Acetic acid test and iodine test		CIN		Total
		Double abnormality	Iodine (-)	CINI	CINII/III	
≤ 30	27	23 (85.2)	3 (11.1)	16 (59.3)	4 (14.8)	20 (74.1)
31–40	31	20 (64.5)	8 (25.8)	17 (54.8)	2 (6.5)	19 (61.3)
41–50	63	27 (42.9)	36 (57.1)	21 (33.3)	5 (7.9)	26 (41.3)
51–60	31	2 (6.5)	27 (87.1)	2 (6.5)	0 (0)	2 (6.5)
> 60	12	0 (0)	11 (91.7)	0 (0)	0 (0)	0 (0)
Total	164	72 (43.9)	85 (51.8)	56 (34.2)	11 (6.7)	67 (40.9)

Age distribution for 164 samples of abnormal test results and CIN

The 164 cases with abnormal colposcopic images were analyzed according to their age. The results showed that the incidence of double abnormality of aceto-white epithelium and iodine negative was higher in the sexual active age group (age ≤ 40 years) and significant lower in menopause or post-menopause group ($\chi^2 = 40.43$, $P < 0.05$). The result was consistent with age distribution of CIN. However, the age distribution for solo abnormality of iodine negative was reversed and the incidence was increasing along with age increase ($\chi^2 = 50.02$, $P < 0.05$), as shown in Table 2.

Discussion

Cervical cancer remains the most common genital female malignancy and invasive cervical cancer is the secondary leading cause of cancer-related mortality in women. Fortunately, cervical cancer is a preventable disease. It has a long latent phase of cervical intraepithelial neoplasia (CIN) which gradually progresses before developing into invasive disease. A key step to prevent invasive cancer is the detection of precancerous lesion by cervical screening and following effective treatment [4].

Routine gynecological exam provides very high diagnosis rate for middle or late stage cervical cancer, and it is very helpful in screening early stage cervical cancer if combined with exfoliative cytology test, including Pap smear test which remains to be considered as a useful, simple, non-invasive and reliable method [4]. However, it is not very helpful toward screening precancerous lesions or carcinoma *in situ*, moreover it comes with relatively high diagnosis missing rate for early stage cervical cancer. The major clinical value of colposcopy is to screen precancerous cervical lesions. Compared to biopsy of suspicious lesions samples collected during routine gynecological exam with naked eye, the biopsy of samples collected *in situ* based on abnormal colposcopic images has the advantage of higher positive screen rate and significant lower diagnosis missing rate. As reported, the diagnosis sensitivity is approximately 80% when using colposcopy to screen CIN, and the specificity is even higher for high

risk CIN grade and early stage cervical cancer [5,6]. Therefore, more and more clinic doctors include colposcopy as the 2nd step of three steps standard operation procedure toward screening precancerous cervical cancer.

Clinically doctors always take medium and high level cervical erosion very seriously, while overlook smooth cervixes. If smooth cervixes samples give negative result for cytology test, no biopsy will be executed. However, it has been reported that CIN happens to smooth cervixes [7]. The so called “smooth cervixes” is only a morphological term and not necessary faithfully demonstrates the inner change of cervixes. Cervical cancer is not always developed from the outermost intraepithelial either. Therefore the cervixes would also be “smooth” at early stage of precancerous cervical cancer, just like CINII and some CINIII carcinoma *in situ*. Cytology test is very useful in diagnosing cervical cancer, still there is missing diagnosis. As a matter of fact, there is true negative cytology and false negative cytology. The true negative cytology means there is no cancer cell at cervical surface, however, the neoplasia might already start to develop from the cervical squamous epithelium, which is CIN. The false negative cytology is the missing diagnosis caused by none-accurate sample collection. The cytology test for so called “smooth cervixes” is lack of target and increases diagnosis missing rate. Moreover, there is “suspicious” non-conclusive result in cytology test. On the other hand, biopsy is the test toward cervixes tissue, rather than some cells, usually targeting at the specific lesions and suspicious lesions with much higher reliability than cytology test. This also explains why some samples with normal cytology test results showed biopsy abnormality in our study. We did colposcopy on 1050 smooth and cytological negative samples and among them we did biopsy on 458 cases. The 68 cases were diagnosed as CIN, including 11 cases high risk CINII/CINIII. Among the 458 cases, 294 showed simple cervical polyps, 164 showed abnormality in colposcopic acetic acid test and/or iodine test, or abnormal glandular opening, dysplasia of the opening of the cervical canal, among which 56 were coincident with cervical polyps. After biopsy we found that only 1 (0.3%) out of 350 simple cervical polyps sample is CIN, while 67 (40.9%) out of 164 colposcopic abnormal samples are

CIN. The result shows that the chance of CIN is much higher for colposcopic abnormal samples than cervical polyps samples. Further analysis shows that the incidence of CIN is higher during sexual active age (≤ 40 years). It is reported by Hang *et al.*, that the incidence of CIN, carcinoma *in situ*, early invasive cancer is 12.08% among sexual active women who are less than 30 years old [7]. There are some reports that though the incidence of early invasive cervical cancer is relatively low, the CIN exists commonly, though the self-resolution rate is high [8,9], and if it is coincident with high risk HPV infection, there is high possibility to develop cervical cancer [10]. Therefore for young women, including the women with normal result of routine gynecological exam, it is necessary to execute colposcopy to screen cervical precancerous lesions and prevent the development of invasive cancer, even for the women with smooth and cytological negative cervixes by optical examine.

The colposcopic image of CIN normally displays aceto-white epithelium, and the stage of aceto-white epithelium change is closely related to CIN [5, 11, 12]. It has highly sensitivity but low specificity, especially for samples with solo aceto-white epithelium. Usually the coincidence with other abnormality would enhance the specificity [6]. The iodine test helps distinguishing suspicious samples. As a result, we use both aceto-white epithelium and iodine negative as biopsy indication. The result showed that for double abnormality samples, the positive predictive rate was as high as 88.9% and the false negative rate was only 3.3%. Besides, the age distribution for double abnormality sample was similar to the distribution for CIN, with high frequency during sexual active age. The results above indicates that the double acetic acid test and iodine test have important clinical meaning. The solo aceto-white epithelium itself is not enough to indicate CIN, while the coincidence of aceto-white epithelium together with other abnormality such as abnormal vein, abnormal glandular opening is more clinical meaningful. The missing diagnosis still exists even for double aceto-white epithelium and iodine negative samples. It indicates that it is better to include vein image and glandular openings as biopsy indication to prevent missing diagnosis.

Though colposcopy is helpful for screening early stage of cervical cancer and precancerous lesions, the related cost increase due to instrument and technology limits its application. Also, it is not realistic to include colposcopy into mass screening. It only fits in hospitals with related facilities and with the approval of patients. Based on related literature [13] and our clinical practice, the indication for colposcopy are as following: (1) abnormal/suspicious result from cytology test (such as ASCUS, AGUS); (2) sus-

picious clinical history, such as contact bleeding; (3) abnormal/suspicious result from gynecological optical exam, such as abnormal or suspicious cervix morphology, abnormal/suspicious acetic acid test or iodine test result; (4) high risk HPV infection; (5) special cases, such as before treatment for cervical lesion, suspicious cervical lesion, before hysterectomy surgery without cytology test result, after hysterectomy surgery and the surgery indication as CIN or higher risk; follow-up after treatment for cervical lesion; (6) if possible perform cross-reference with cytology test. Using colposcopy reasonably could guarantee its effectiveness and avoid the waste of hospital facility and release the concern of patients.

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