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Study of clinical diagnosis of cervical glandular intraepithelial neoplasia

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Summary

Objective: To preliminarily evaluate the clinical significance of different methods in diagnosis of cervical glandular intraepithelial neoplasia (CGIN). *Materials and Methods:* Clinical manifestations, ThinPrep cytologic test (TCT), cervical biopsy, and pathological features of 106 patients with CGIN admitted to Beijing Obstetrics and Gynecology Hospital between 2008 and 2011 were retrospectively analyzed. *Results:* Among 146 cases diagnosed with CGIN, 87 (59.6%) had L-CGIN and 59 (40.4%) H-CGIN. Thirty-seven patients (25.6%) were found to have simple CGIN and 109 (74.6%) had CGIN complicated with cervical intraepithelial neoplasia (CIN). TCT revealed atypical glandular cells (AGC) in 20 patients (13.7%), six of whom had L-CGIN (6.9%) and 14 (23.7%) had H-CGIN with statistical significance between two groups ($p < 0.05$). TCT detected AGC in 13 cases (35.1%) with simple CGIN and seven with mixed CGIN (6.4%) ($P< 0.05$). Endocervical curettage (ECC) revealed AGC abnormality in ten cases (25.6%). Cervical biopsy under colposcope revealed 32 patients (22.9%) had CGIN, including 15 L-CGIN (18.3%), and 17 H-CGIN (29.3%) with no statistical significance ($p > 0.05$). Among those diagnosed with CGIN by colposcope-assisted cervical biopsy, 19 (51.4%) had simple CGIN and 13 (11.9%) mixed CGIN ($p < 0.05$). *Conclusion:* Preoperative diagnostic rate of simple CGIN was higher than CGIN complicated with CIN.

Key words: Cervical glandular intraepithelial neoplasia; Endocervical glandular dysplsia; Diagnosis.

Introduction

Recently, the incidence of cervical adenocarcinoma has been increasing and the onset age is becoming younger, approximately accounting for 10%-34% of cervical cancer [1]. Cervical glandular intraepithelial neoplasia (CGIN) is precancerous lesions of adenocarcinoma and is less understood compared with cervical intraepithelial neoplasia (CIN). This study was designed to preliminarily evaluate the clinical significance of different methods in diagnosis of 146 CGIN patients admitted to the present institution from 2008 throughout 2011.

Materials and Methods

Study subject

A total of 146 patients were diagnosed with CGIN and admitted to Beijing Obstetrics and Gynecology Hospital between January 2008 and May 2011. Among them, 117 were surgically treated with cervical conization, 23 loop electrosurgical excision procedure (LEEP), and six panhysterectomy. Thirty-two patients were diagnosed with CGIN by preoperative histological examination and 114 diagnosed with CGIN postoperatively including those with CGIN complicated with CIN. Those subjects complicated with cervical squamous carcinoma and cervical adenocarcinoma were excluded from this study. All cases were aged between 22 and 67 years, 41.3 years on average.

The mean times of pregnancy were 2.5 and of delivery was 1.6. Those with menopause accounted for 15.8% and 84.2% of premenopausal women. Eighty-eight patients (60.2%) had no clinical symptoms, 25 cervical contact hemorrhage, 19 abnormal secretion, and nine abnormal vaginal bleeding. All cases with CGIN were confirmed by pathological examination.

Methods

All 146 patients underwent ThinPrep cytologic test (TCT) preoperatively. Those with AGC and undesirable transformation zone further received colposcope and cervical biopsy. Those suspected with AGC received endocervical curettage (ECC) simultaneously. Based upon histological examination, cervical conization was subsequently performed as necessary. Another ten patients with non-cervical lesions were diagnosed with CGIN by postoperative pathological examination. CGIN refers to glandular neoplasia of cervix during early stage of infiltration, divided into two levels: low-grade cervical glandular intraepithelial neoplasia (L-CGIN) and high-grade cervical glandular intraepithelial neoplasia (H-CGIN). H-CGIN included in situ adenocarcinoma.

Classification of CGIN was conducted based upon histological and cytological characteristics. Histological manifestations of H-CGIN resembled in situ adenocarcinoma. L-CGIN was characterized with certain abnormal changes. H-CGIN referred to all abnormal alterations.

Statistical analysis

SPSS 13.0 statistical software was utilized for data analysis. Chi-square and paired chi-square tests were performed. $P < 0.05$ was considered as statistical significance.

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Table 1. — *TCT outcomes.*

TCT results	Cases	AGC	non-AGC	*p* value
L-CGIN	87	6	81	< 0.05
H-CGIN	59	14	45	
Simple CGIN	37	13	24	< 0.05
Mixed CGIN	109	7	102	

Table 2. — *Cervical biopsy under colposcope in the diagnosis of CGIN of different grade*

CGIN classification	Cases	Cervical biopsy under colposcope	
		CGIN	Without CGIN
L-CGIN	82	15	67
H-CGIN	83	17	41
Total	140	32	108

Table 3. — *Relationship between preoperative and postoperative diagnosis of CGIN*

Preoperative diagnosis	Cases	Postoperative diagnosis	
		Simple CGIN	Mixed CGIN
CGIN	32	19	13
Without CGIN	114	17	96
Total	146	37	109

Results

Types of CGIN

Among 146 cases of CGIN, 37 (25.6%) had simple CGIN and 109 (74.4%) mixed CGIN, mainly complicated with CIN. Eighty-seven (59.6%) were diagnosed with L-CGIN and 59 (40.4%) with H-CGIN.

TCT

TCT revealed signs of AGC in 20 cases (13.7%), including six (6.9%) with L-CGIN and 14 (23.7%) H-CGIN; statistical significance was observed between two groups ($p < 0.05$). The detection rate of H-CGIN was significantly higher than L-CGIN by TCT. Among 37 cases diagnosed with AGC, 13 (35.1%) had simple CGIN and seven (6.4%) mixed CGIN with statistical significance ($p < 0.05$). The detection rate of TCT in simple CGIN was higher than that in mixed CGIN. The outcomes of TCT are illustrated in Table 1.

Comparison of colposcope-assisted cervical biopsy, ECC, and postoperative cervical pathological examination results

Among 146 cases, 140 underwent cervical conization. Preoperative cervical biopsy revealed 32 (22.9%) CGIN and 108 (77.1%) were diagnosed with postoperative cervical conization. These 140 patients received colposcope and cervical biopsy. Thirty-nine patients with AGC and poor transformation zone were treated with ECC. ECC revealed gland cell abnormality in ten cases (25.6%). Thirty-two patients (22.9%) were diagnosed with cervical biopsy including 15 L-CGIN (18.3%) and 17 H-CGIN (29.3%) ($\chi^2 = 2.339$, $p > 0.05$) Cervical biopsy revealed 19 cases (51.4%) had simple CGIN and 13 mixed CGIN (11.9%) ($\chi^2 = 26.259$, $p < 0.05$), as shown in Tables 2 and 3.

Discussion

CGIN and epidemiological characteristics

As the precancerous lesions of cervical adenocarcinoma, the naming and category of CGIN remain debated. In the USA and other regions, the classification criteria proposed by International Society of Gynecological Pathologists were adopted, that is, endocervical glandular dysplasia (EGD) and in situ adenocarcinoma. In the U.K. and European nations, it is named as cervical glandular intraepithelial neoplasia (CGIN), which is divided into two categories: low-grade CGIN (L-CGIN) and high-grade CGIN (H-CGIN). H-CGIN includes in situ adenocarcinoma [2]. Some scholars classified CGIN into CGIN I, II, and III. However, it is challenging to implement this standard and the diagnostic reproducibility is low in clinical practice [3]. The European classification criteria of CGIN were adopted in this study. CGIN is less commonly seen than CIN.

The ratio of cervical adenocarcinoma and squamous carcinoma is 1:5, whereas the ratio of precancerous lesions of these two cancers was 1:80 [4]. The ratio of in situ cancer and infiltrated cancer was 1:3 for adenocarcinoma and 5.25 : 1 for squamous carcinoma, and 62 (58.5%) were diagnosed with L-CGIN and 44 (41.5%) with H-CGIN. The age at onset of CGIN was 39-40 years, 39.89 years on average [5]. The mean age in this study was 41.3 years, basically consistent with previous findings. It is difficult to diagnose CGIN during early stage. Previous studies demonstrated that HPV infection is closely correlated with cervical gland lesions. HPV 16, 18, and 31 can be detected in over 80% of patients diagnosed with cervical adenocarcinoma and squamous carcinoma. However, the underlying cause remains elusive. Previous studies indicated the time of L-CGIN progressing into H-CGIN was 1.5 to three years [6]. It has been reported that HPV16 is associated with cervical in situ adenocarcinoma, and HPV18 is associated with advanced cervical adenocarcinoma [7]. In this study, 87 cases (59.6%) were diagnosed with L-CGIN and 59 (41.5%) H-CGIN. A majority of cases (60.2%) had no symptoms. Others presented with clinical symptoms mainly including vaginal secretion abnormality and contact hemorrhage.

Diagnosis of CGIN

It is a challenging task to diagnose CGIN preoperatively. A majority of CGIN is diagnosed after cervical biopsy, cervical conization or uterus excision. Previous studies indicated that approximately 46% to 72% of CGIN patients were diagnosed after excision of CIN lesions [4]. Zhang *et al.* reported that 66.7% of CGIN cases were confirmed after

treatment of CIN or benign pathological changes. In this clinical trial, the percentage of postoperative diagnosis of CGIN was 80.3%, which is consistent with previous findings. It is difficult to diagnose CGIN preoperatively due to the following reasons: 1) CGIN lesions were mainly distributed around the cervix and affected the superficial mucosa, recess gland, deep gland, CIN, SCCA, and adenocarcinoma margins. It is likely to miss diagnosis due to difficult sampling. 2) CGIN cells, endocervical cells, and endometrial cells resembled in appearance. It was difficult to differentiate from cervical squamous epithelial lesions, possibly leading to misdiagnosis. 3) CGIN is constantly complicated with CIN. Previous studies reported that up to 90% of non-infiltrated pathological changes were complicated with squamous epithelial CIN [8]. The proportion of CGIN complicated with CIN was 74.4% in this study. Severe CIN lesions may conceal the pathological changes of CGIN, mainly characterized with CIN lesions. Therefore, it is likely to miss the diagnosis of CGIN.

Diagnostic levels of pathologists

The Bethesda system (TBS) is widely applied in clinical screening of cervical pathological changes and significantly enhances the early diagnosis of cervical squamous epithelial lesions. However, the positive rate of TBS in screening of cervical lesions is low and the false-negative rate is high, which is likely to cause misdiagnosis. In addition, the detection rate of cervical AGC is equally low ranging from 0.05% to 2.1% [9]. It has been reported that the sensitivity of TCT ranged from 32.7% to 48.1%, and the specificity was 69.4%-94.4% [10]. Zhang *et al.* demonstrated the sensitivity of TCT was 33.3% in Chinese population [11]. In this study, merely 13.7% of patients presented with preoperative TCT abnormality, probably due to the majority of CGIN cases complicated with CIN, which affected the accuracy of TCT. The detection rate of L-CGIN by TCT was 6.9% (6/87) and 23.7% (14/59) for H-CGIN cases with statistical significance, suggesting that the positive rate of TCT in screening of H-CGIN is higher than L-CGIN. TCT remains the only screening approach of CGIN, whereas the sensitivity is relatively low. However, colposcope-assisted cervical biopsy and ECC have their own limitations in diagnosis of CGIN.

It is difficult to collect sampling of the lesions within the cervix under colposcope. The subjective judgement of the physicians is also likely to cause miss diagnosis. Additionally, use of ECC fails to collect the samples and the possibility of extracervical lesions could not be excluded. In this study, 39 patients received ECC, and only ten cases (25.6%) were found to have AGC, hinting a low preoperative diagnostic rate. Previous studies demonstrated that the positive predictive value of colposcope in diagnosis of squamous and glandular epithelial lesions was 93.5%, whereas 9.8% for the diagnosis of glandular epithelial lesions [12]. Other studies reported that the detection rate of glandular abnormality ranged from 35% to 70% in CGIN patients by colposcope-assisted cervical biopsy [9]. In this study, colposcope-assisted biopsy revealed glandular epithelial abnormality in 22.8% of patients and the sensitivity was not high. No statistical significance was observed in diagnostic rate of varying degree of CGIN. TCT revealed that those with AGC should undergo colposcope and cervical biopsy under direct vision to avoid the miss diagnosis. Cervical conization is of vital value in the diagnosis of CGIN.

CGIN lesions were distributed in a central and diffusive pattern, approximately 10% of CGIN lesions were located above the cervix [13]. Compared with CIN, it is more complex and difficult to diagnose CGIN. TCT and colposcope examination lack reliability. Cervical conization rather than cervical biopsy should be performed in diagnosing patients suspected with cervical glandular diseases. Kietpeerakool *et al.* [14] reported that among 51 patients diagnosed with cervical in situ adenocarcinoma by cervical conization, 22 presented with cervical glandular abnormality, 29 squamous epithelial abnormality, and 9 AGC by colposcope-assisted biopsy and/or ECC. Thirty-one patients (60.8%) were suspected with glandular diseases before surgery. Previous studies demonstrated that pap smear, colposcope-assisted biopsy, and ECC were not suitable for diagnosing cervical glandular diseases, whereas cervical conization should be considered. In this study, 140 patients underwent cervical conization including 32 (22.9%) diagnosed with glandular lesions preoperatively and 108 confirmed by pathological diagnosis following cervical conization. Therefore, cervical conization plays a pivotal role in the diagnosis of CGIN.

Preoperative diagnostic rate of simple CGIN higher than mixed CGIN

Majority of CGIN patients were complicated with CIN lesions and the percentage of simple CGIN was relatively low. CGIN patients complicated with CIN revealed that they were characterized with squamous epithelial lesions prior to examination whereas glandular epithelial pathological changes were neglected. Thus, preoperative detection rate of mixed CGIN was lower than simple CGIN. Ovanin-Rakic *et al.* [15] demonstrated that among 123 CGIN cases, 13 had adenocarcinomas in situ of the cervix (AIS), 18 glandular intraepithelial lesions (GIL) I and II, 58 AIS complicated with squamous epithelial lesions, and 34 AIS complicated with GIL I and II. The detection rate of simple AIS, GIL I, and II was 61.5% and 22%, significantly higher compared with 25.9% and 20.6% for mixed cases. Kietpeerakool *et al.* [14] reported that 20 (70.4%) among 51 cases with AIS were suspected with simple glandular lesions preoperatively, whereas 12 AIS patients (50%) were complicated with CIN. Preoperative detection rate of simple AIS was higher than that of mixed AIS. In this study, TCT revealed the signs of AGC in 37 patients (35.1%) with simple CGIN, and seven cases (6.4%) with mixed CGIN with statistical significance ($p < 0.05$). Thus, the detection

rate of AGC by TCT in simple CGIN was significantly higher than mixed CGIN. Thirty-two cases were diagnosed with CGIN by colposcope-assisted cervical biopsy including 19 (51.4%) simple CGIN and 13 (11.9%) mixed CGIN with statistical significance ($p < 0.05$), suggesting that it is much easier to identify simple CGIN than mixed CGIN. Taken together, it is difficult to preoperatively diagnose CGIN. TCT remains the only screening approach of CGIN with relatively low sensitivity. Colposcope, cervical biopsy/ECC present with a low detection rate of CGIN. For CGIN patients complicated with CIN, conventional colposcope and endocervical curettage should be performed to detect AGC. For those suspected with glandular epithelial abnormality, cervical conization should be performed to confirm the diagnosis. How to screen and diagnose CGIN during early stage and before surgery remains a challenge. Along with the improvement of cervical sampling and cell molecular diagnosis and deeper understanding of clinical and pathological physicians, preoperative detection rate of CGIN is increased, thereby reducing the incidence and mortality of infiltrated cervical adenocarcinoma.

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