A Prospective Study on the Application of Endometrial Cytology Examination in the Screening of Endometrial Cancer

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Abstract: *Background*: Endometrial cancer is one of the most common gynecology malignancies. But there is still lack of an accurate, reliable, convenient, easy, economical and practical method for early detection of endometrial cancer and precancerous lesions. The aim of this study is to evaluate the specimen quality and diagnostic accuracy of endometrial cytology examination in the screening of endometrial cancer.

Methods: 95 patients with abnormal uterine bleeding or vaginal ultrasound examination results indicating intrauterine abnormalities and needing endometrial examination were investigated, and specimens were collected using endometrial sampling device for cytology (ESDC) and sliced using thinprep cytology test (TCT), meanwhile, hysteroscopy auxiliary diagnostic curettage and histopathological examination were performed.

Results: The satisfaction rate was 100% for the specimens collected using ESDC and 97.9% for those using diagnostic curettage. The difference in the satisfaction rate of collecting specimens was statistically significant between the two methods, and the satisfaction rate of collecting specimen using endometrial cytology was superior to that using diagnostic curettage. Taking diagnostic curettage histopathologic results as "gold standard", the sensitivity of endometrial cytology was 63.6%, specificity 93.6%, positive predictive value 70% and negative predictive value 95.2% in the screening of endometrial cancer.

Conclusion: Endometrial cytology can be used as a reliable, safe and simple method in the screening of endometrial cancer.

Keywords: Endometrial cytology, endometrial sampling device for cytology, endometrial cancer, thinprep cytology test.

INTRODUCTION

Endometrial cancer is one of the most common malignancies of female genital tract, accounting for 20%~30% of the female genital tract malignancies, and its incidence takes the first place among gynecological malignancies in Europe and North America [1]. However, there is still lack of an accurate, reliable, convenient, easy, economical and practical method for early detection of endometrial cancer and precancerous lesions and timely intervention in the screening of endometrial cancer. Some scholars have performed studies on endometrial cytology in the screening of endometrial cancer [2]; application of thinprep cytology test (TCT) for making slice further improves the feasibility and accuracy of cytology in endometrial cancer screening [3, 4]. In this study, the advantages and disadvantages of the two methods by using SAP-1 endometrial sampling device for cytology (ESDC) to collect endometrium and TCT to make slice, and endometrial fractional curettage to obtain tissue specimen pathology as "gold standard" with the aid of hysteroscopy were compared to investigate the feasibility and clinical value of endometrial cytology examination for endometrial cancer screening.

METHODS

From June 2013 to September 2014, a total of 95 patients aged from 23 to 72 years old with a mean of 45.8 were diagnosed as infertility, polycystic ovary syndrome, abnormal vaginal bleeding, obesity, hypertension, diabetes, oral tamoxifen, hormone replacement therapy, delaying closing menstruation and other risk factors in the Second People's Hospital of Zhaoqing, Guangdong Province. All patients were preoperatively informed consent in the endometrial cytology examination followed by fractional curettage. This study was approved by the local ethics committee.

SAP-1 ESDC (Beijing Jiuzhou Qingyuan Technology Development Co., Ltd; Chaoyang district Beijing 100023 China), it has a jacket tube. The frond-end collecting ring is 25mm in length and 3mm in diameter, and the collecting ring can be hidden in

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jacket before and after sampling to avoid contamination.

The patients were placed in the bladder lithotomy position for hysteroscopy, followed by routine disinfection, and then endometrial cells were collected before the probe gets into the uterine to avoid contaminating cervical cells. ESDC was inserted into uterine fundus slowly under the protection of jacket tube, and jacket tube was retracted to expose collecting ring, clockwise 10 turns, collecting ring was taken back, then ESDC exited from the cervix. Collecting ring was fully rinsed in SurePath cell preservation solution (US BD Company). Thin prep liquid-based cytology smears was prepared by sedimentation TCT technology, the cytology specimens was centrifuged to remove impurities and excess inflammatory cells, then the cell was transferred to a settling chamber, embedded in glass slides, fixed with 95% alcohol and routine Papanicolaou staining. Then, histological specimens were obtained by the method of hysteroscopy assisted fractional curettage, fixed by 10% formalin conventionally, embedded in paraffin and HE stain. The results of thinprep cytology smears were reviewed by two cytological diagnosis professionals independently.

Patient's chief complaint, history of present illness, past history, location and depth of the uterine cavity, use history of collector, amount of bleeding and patient's subjective feeling were recorded in detail; meanwhile, the above information was recorded when diagnostic curettage was performed.

Satisfactory criteria of specimens: (1) clearly marked; (2) the relevant clinical data are accurate and complete; (3) having a sufficient number of well-preserved endometrial glandular epithelial cells (it should have at least 5-6 heaps of endometrial cell excepting endometrial cell); (4) specimens containing abnormal cells will be judged as satisfactory. Unsatisfactory criteria: (1) lack of clear markers; (2) slide is broken and beyond repair; (3) cells overlapped excessively, blood and inflammatory cells covering the endometrial cells, poor quality of fixed specimen, excessive dryness, contamination and others affecting the observation of more than 75% gland cells.

Endometrial cytology diagnostic criteria can be classified into 4 categories based on home and abroad literature: (1) no intraepithelial lesions and malignant cells (only endometrial cells in proliferating, secretory or atrophic phases were observed); (2) benign proliferative changes [including simple hyperplasia, complex hyperplasia, irregular proliferation (lesion is between proliferating and simple phases and can be regarded as a part of regional simple hyperplasia) and endometrial polyps]; (3) atypical endometrial hyperplasia(including atypical endometrial hyperplasia and endometrial intraepithelial neoplasia); (4) endometrial cancer (including endometrioid adenocarcinoma, mucinous adenocarcinoma, papillary serous adenocarcinoma and clear cell carcinoma). Results of histopathological slices were reviewed by two pathology professionals independently. The surgeon will judge the sample that aren't sent for testing due to small quantity of the tissues collected by curettage or the sample that were sent for testing but is not sufficient to make a histopathologic diagnosis as unsatisfactory. Diagnostic curettage endometrial pathology can be grouped into four categories: normal endometrium, benign, precancerous lesions and endometrial cancer. Cytology results as atypical endometrial hyperplasia and endometrial cancer was defined as positive criteria for screening of endometrial cancer, histopathological diagnosis was taken as "gold standard".

Statistics

SPSS 13.0 software was used for statistical analysis, t test and X^2 test were performed, and the difference was statistically significant if $P<0.05$.

RESULTS

In the 95 patients, satisfaction rate was 100% (95/95) for the specimens collected using endometrial cytology; and 97.9% (93/95) for those using diagnostic curettage, of which two patients were unsatisfactory as the quantity of curetted tissues was too small to be sent for testing. Comparing the two methods, the satisfaction rate of collecting specimen using endometrial cytology was superior to that using diagnostic curettage, and the difference was statistically significant ($\chi^2=93$, $P < 0.05$).

In this study, 93 patients had results of both endometrial cytology and histopathology (97.9%, 93/95). Six patients with endometrial cancers (6.5%, 6/93) and four patients with atypical endometrial hyperplasia (4.3%, 4/93) were observed through endometrial cytology examination. Six patients with endometrial cancers (6.5%, 6/93), five patients with atypical endometrial hyperplasia (5.4%, 5/93), 19 patients with benign endometrial lesions (including

Table 1: Comparison of 93 Patients with both Endometrial Cytology and Histopathology

Cytology results	Histopathological results				Total
	No abnormal	Benign lesion	Atypical hyperplasia	Endometrial cancer	
No intraepithelial and malignant lesions	60	19	4	0	83
Benign endometrial hyperplasia	0	0	0	0	0
Atypical endometrial hyperplasia	2	0	1	1	4
Endometrial cancer	1	0	0	5	6
Total	63	19	5	6	93

simple hyperplasia, complex hyperplasia, irregular hyperplasia and endometrial polyps) (20.4%, 19/93) were observed through both hysteroscopy and histopathological. See Table **1**.

Of the six patients pathologically diagnosed as endometrial cancer, five had consistent results in cytology and pathology, and one was diagnosed as atypical endometrial hyperplasia through cytology. Of five patients pathologically diagnosed as atypical endometrial hyperplasia, one had consistent results in cytology and pathology, and four were diagnosed as no intraepithelial neoplasia.

Of the six patients whose endometrium cytologically diagnosed as endometrial cancer, five were pathologically confirmed as endometrial cancer and one as normal endometrium. Of the four patients whose endometrium cytological diagnosed as atypical hyperplasia, one was pathologically confirmed as atypical endometrial hyperplasia, one as pathological endometrial cancer and two without abnormality.

The endometrial cytology results as atypical endometrial hyperplasia or endometrial cancer was defined as positive criteria for screening of endometrial cancer, histopathologic diagnosis of endometrium obtained with hysteroscopy and fractional curettage was taken as "gold standard", and statistical analysis was performed. Sensitivity of endometrial cytology for screening of endometrial cancer was 63.6% (7/11), specificity 96.3% (79/82), positive predictive value of 70% (7/10), and negative predictive value 95.2 % (79/83) (see Table **2**). The results of two diagnostic methods were analyzed using χ^2 test (see Table **3**), and the difference was not statistically significant (χ^2=0, P>0.05).

DISCUSSION

Endometrial cancer is the most common form of gynecology carcinoma. However, there is no reliable screening test for its early detection. Currently, the screening method for endometrial cancer is mainly transvaginal ultrasound (TVS), which has an advantage

Table 2: Diagnostic Accuracy of Endometrial Cytology in the Screening of Endometrial Malignant Lesions

Endometrial cytology	%	95% confidence interval
Sensitivity	63.6	53.8-73.4
Specificity	96.3	92.5-100
Right index	59.9	49.9-69.9
Positive predictive value	70	60.74-79.26
Negative predictive value	95.2	90.88-99.5

Table 3: Correlation of Endometrial Cytology and Diagnostic Curettage Pathology

Cytology	Diagnostic curettage pathology		Total
	Positive	Negative	
Positive	7	3	10
Negative	4	79	83
Total	11	82	93

in detecting endometrial thickness, lesion size, location and depth of myometrial invasion of endometrial cancer [5]. However, according to the literature, sensitivity of ultrasound for diagnosis intrauterine lesions was 54.2% [6].

In this context, endometrial cytology test (ECT) has emerged. Scholars have performed studies on endometrial cytology examination for the observation of endometrial cancer lesions and screening of endometrial cancer, and have achieved a positive result. In 2002, Nakagawa-Okamara *et al.* [2] retrospectively analyzed the data of 1195 patients with endometrial cancer from 22 hospitals in Japan from 1989 to 1997, of which, 1069 patients were detected through general outpatient clinics and 126 patients through ECT screening. The stage of endometrial cancer was confirmed was significantly later in outpatient group than that in screening group, for the proportion of Stage I was 74.4% and 61.0%, respectively; and five-year survival rate in outpatient group was significantly lower than that in screening group (84.3% & 94.0%). Studies had shown that screening of endometrial cancer in postmenopausal asymptomatic population helps early detection of endometrial cancer and prolongs survival. In recent years, some Chinese scholars also carried the study on endometrial cytology in the screening of endometrial cancer. The results showed that the sensitivity of this method was good (81.8% -87.5%) and the specificity was high (91.9% -100.0%) [5, 7]. However, endometrial cytology has not yet been widely recognized by pathologist and gynecologist, because the morphological change of endometrium is associated with hormone levels, and the interference of inflammatory cells, overlap and blood cells makes it difficult to review the slice, as well as the operation for sampling and smear also affects the results.

When TCT technology was applied in cervical cytology screening, it made the specimen collection, fixing, transfer, preparation process more repeatable, the screening more standard, and laid the foundation to develop a standard cytology method. TCT technology, when applied in the screening of endometrial cytology, may improve the probability of cytology for the screening of endometrial cancer. And this study had been performed with good results. Remondi *et al.* [8] using ESDC (Endoflower sampler) combined with TCT technology, performed cytology examination for 98 patients with irregular vaginal bleeding or asymptomatic postmenopausal women, and pathological diagnosis of hysteroscopic endometrial biopsy was taken as "gold standard". The sensitivity of cytological screening for endometrial lesions was 92%, specificity 95% and diagnostic accuracy 93.5%. Kipp *et al*. [9] performed the examination for 139 patients using the same method, and the results showed that the sensitivity was 95% and specificity was 66%; Buccoliero *et al*. [10] also studied a large sample size using the same method in 917 patients enrolled, the sensitivity was 96% and the specificity was 66%. Recently, a retrospective study [11] assessed the correlation between cytopathology and histopathology to evaluate the diagnostic value of cytology for endometrial cancer. 1,361 control and 1,441 endometrial cancer cases were analyzed. Endometrial cytology detected cancer in 1,279 (916 positive and 363 suspicious) cases with a sensitivity (positive plus suspicious cases) of 88.8% and a specificity of 98.5%. These findings proves the efficacy of endometrial cytology from another perspective. In our study, the sensitivity of ESDC combining with TCT technology for the diagnosis of endometrial cancer was 63.6% (7/11), the specificity 96.3% (79/82), positive predictive value 70% (7 / 10) and negative predictive value 95.2% (79/83). And the diagnostic sensitivity was slightly lower than the results of other studies, but equal to the sensitivity of cervical Pap smear (60-70%). In this study, the results suggest that endometrial cytology examination has a broad application prospect in the screening endometrial cancer and precancerous lesions.

The method of obtaining specimen using ESDC is simple and convenient, without cervical dilation and anesthesia, and can be carried out at the outpatient clinic. In addition, patients have a good tolerance and compliance for the examination. Therefore, it is suitable for large-scale screening in high-risk populations and long-term monitoring in individuals. TCT technology has greatly improved the quality of cell smears, such as clean background of thin layer smear, uniform cell distribution, clear structure, well preserved morphology, less overlap, the intervention significantly less than the ordinary smear (especially the extrusion and interference in tumor cells), easier to review the slice, making recognition of tumor cells more accurate. But endometrial cytology method still has its limitations: (1) it may sometimes cause misdiagnosis for localized lesions in large uterine cavity, bottom of the uterus and uterine corner since the examination is to check uterine cavity exfoliated cells. In this study, three patients with atypical endometrial hyperplasia were missed diagnosis, one was suspected malignancy and needed

further immunohistochemistry assisted diagnosis. (2) Due to the influence of hormone drugs, serious infections, intrauterine device and cervical cell contamination, the false positive rate is higher. In this study, three patients had over-diagnosis, of which, one with functional uterine bleeding was diagnosed as endometrial mild dysplasia, one ovarian cancer patient's endometrial in senile change was diagnosed as adenocarcinoma, and one cervical cancer patient's endometrial in normal proliferating was diagnosed as endometrial malignancy. (3) Change of endometrial morphology is associated with hormone levels, and cytology sampling time can affect the judgment of cytology results. In summary, endometrial cytology is currently only available as a preliminary screening tool for endometrial malignant transformation, and a combination of histopathological examination is also required for further confirmed diagnosis.

In conclusion, even though endometrial cytology has its defects, given that the disadvantage of current examinations for diagnosis intrauterine lesions and advantage of endometrial cytology examination. Endometrial cytology examination has a practical application prospect in the screening endometrial cancer and precancerous lesions.

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