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Original Article

Liquid-based endometrial cytology associated with curettage in the investigation of endometrial carcinoma in postmenopausal women

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ABSTRACT

Objective: The aim of this study was to investigate the diagnostic accuracy of liquid-based endometrial cytology in postmenopausal women, in comparison with histology.
Materials and methods: There were 790 postmenopausal women scheduled for hysteroscopy enrolled in this study. After providing informed consent, all patients proceeded sequentially through endometrial cytology, hysteroscopy, and then dilatation and curettage (D&C). Cytology sampling was performed by brushing the uterus cavity using SAP-1 and the sample was prepared to liquid-based smear using SurePath technology. The slides were stained by Papanicolaou method. All cytological diagnoses were correlated with the D&C histological diagnoses.
Results: Cytohistological correlations were possible in 567 (71.8%) patients: the D&C was inadequate in 204 (25.8%) patients; the cytology was inadequate in 32 (4.1%) patients; and both were inadequate in 13 (1.6%) patients. SAP-1 provided more sufficient material for cytology than D&C can for histology ($p < 0.001$). Taking atypical hyperplasia and endometrial carcinoma as a positive result, the diagnostic accuracy of liquid-based endometrial cytology was 81.5%; sensitivity was estimated at 75.9%, specificity at 83.3%, positive predictive value at 59.1% and negative predictive value at 91.6%.
Conclusion: Liquid-based endometrial cytology can be considered a useful method in the detection of endometrial pathology in postmenopausal women.

Introduction

Endometrial carcinoma is the most common malignancy of the female genital tract in developed countries [1]. It often occurs in postmenopausal women and abnormal vaginal bleeding is the primary symptom. There are several methods to identify the endometrial pathology, such as transvaginal ultrasonography (TVS), hysteroscopy and endometrial biopsy, sonohysterography and endometrial cytology [2–5]. TVS is known as the first step in the evaluation of women with postmenopausal bleeding. However, TVS suffers from low specificity, due to its low positive predictive value (PPV) and high false-positive rate [6]. Hysteroscopy and dilatation and curettage (D&C) is a second-line method that has been considered as the 'gold standard' in the diagnosis of endometrial pathology.

Historically, endometrial cytology has not been widely used for accuracy issues, which is probably due to the common presence of excess blood and overlapping cells [7]. Recent development of liquid-based cytology techniques can overcome these obstacles and increase the diagnostic accuracy [8–10]. We conducted the current study to compare the results of liquid-based endometrial cytology with hysteroscopy and D&C to assess its diagnostic accuracy in a group of 790 postmenopausal women.

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Materials and methods

Patients enrolled in this trial were 790 postmenopausal women who received hysteroscopy from March 2009 to February 2015. This multicenter study was performed in the Department of Gynecology of Peking University First Hospital, Beijing Tsinghua Changgung Hospital, Beijing Cancer Hospital, and Beijing Daxing District Hospital. After providing informed consent, all the patients proceeded sequentially to endometrial cytological sampling, hysteroscopy, and diagnostic and/or therapeutic D&C. The median age of the patient group was 54 years (range, 41–89 years). The majority of the cases, 334 women (42.3%), hysteroscopy was required for abnormal endometrium assessed by transvaginal ultrasonography as follows: thickened endometrium ($\geq$ 5 mm) or intrauterine occupational disease. There were 193 women (24.4%) referred for postmenopausal uterine bleeding; 228 women (28.9%) were referred for both postmenopausal bleeding and abnormal endometrium. Twenty-two women (2.8%) were tamoxifen users. Eight women (1.0%) received hysteroscopy follow-up who were diagnosed with simple or complex endometrial hyperplasia. Five women (0.6%) women were referred for atypical glandular cells found in ThinPrep Cytologic Test (TCT) (Table 1). There was no financial interest or any arrangement with the companies producing the instruments used in the study.

The device used for endometrial cytological sampling was the SAP-1 device (Saipujiuzhou, Beijing, China; Figure 1). This device was patented and received permission to be used in China. The SAP-1 sampler measures 3 mm in diameter and 250 mm in length. It consists of a flexible latex loop with spines on the side and a smooth tip to prevent injury to the myometrium. There is an outer protective sheath outside the loop to prevent contamination from cervical and vaginal cells. Before using the device, the stem was withdrawn into the sheath, and it was inserted into the uterus cavity through the endocervical canal. The loop was then released and rotated clockwise and anticlockwise, thus collecting tissue on the edges of the curette. It was then withdrawn into the sheath to prevent cervical contamination. After the device was removed from the uterus, the loop with the specimen was exposed and immersed in a SurePath (BD Diagnostic, Burlington, NC, USA) vial and vigorously rotated to allow the cells to release. The vial was labelled with the patient information and transported to the Department of Cytopathology. With a succession of centrifugation and suspension to obtain mucolysis and hemolysis, blood and mucus were separated from the endometrial cells. Finally, the vial was processed using AutoCyte PREP automated slide processor (Tri-Path; Becton–Dickinson, Franklin Lakes, NJ, USA). The slides were stained with routine Papanicolaou stain.

Hysteroscopy was performed using a 5-mm optic with saline solution distension after the cytological sampling. Histologic sampling was performed by D&C. Endometrial samples were routinely fixed in neutral buffered formalin, embedded in paraffin, and stained with hematoxylin–eosin.

Cytological and histological diagnosis was done by two pathologists blindly. The slides were considered unsatisfactory samples when there were fewer than five evaluable endometrial clusters (endometrial cytology) or severe fragmentation or scarcity of the endometrial tissue (D&C). If the first cytological or histological slide was inadequate, a second one would be prepared. When the second one was also an unsatisfactory sample, the diagnosis was considered as *inadequate*.

The cytological criteria used in the cellular interpretation were according to a previously published diagnostic system [11]. The cytological findings were divided into four categories: normal endometrium, benign endometrial abnormality, atypical endometrial cell, and suspected endometrial carcinoma (Figure 2). Negative and benign endometrial abnormality was considered as negative results, and atypical endometrial cell and suspected endometrial carcinoma were considered as positive results. The histological diagnosis was given according to the World Health Organization criteria of 2003 [12]. All cytological diagnoses were correlated with the D&C histological diagnosis.

Statistical analysis was carried out using SPSS 10.0 for Windows (SPSS Inc. Chicago, IL, USA). A double access table was created to evaluate the sensitivity of cytology (true positive/all positive

Table 1
Distribution of patients according to inclusion criteria.

Inclusion criteria	No. of patients	Endometrium thickness (mm), mean ± standard deviation (range)
Thickened endometrium	334	8.15 ± 3.15 (5–23)
Thickened endometrium + AUB	228	7.50 ± 2.50 (5–20)
AUB	193	2.20 ± 1.12 (1–4)
Tamoxifen users	22	7.15 ± 3.85 (4–18)
Simple or complex endometrial hyperplasia follow up	8	9.25 ± 5.00 (5–20)
Atypical glandular cells found in TCT	5	6.12 ± 3.75 (5–12)

AUB = abnormal uterine bleeding; TCT = ThinPrep Cytologic Test.

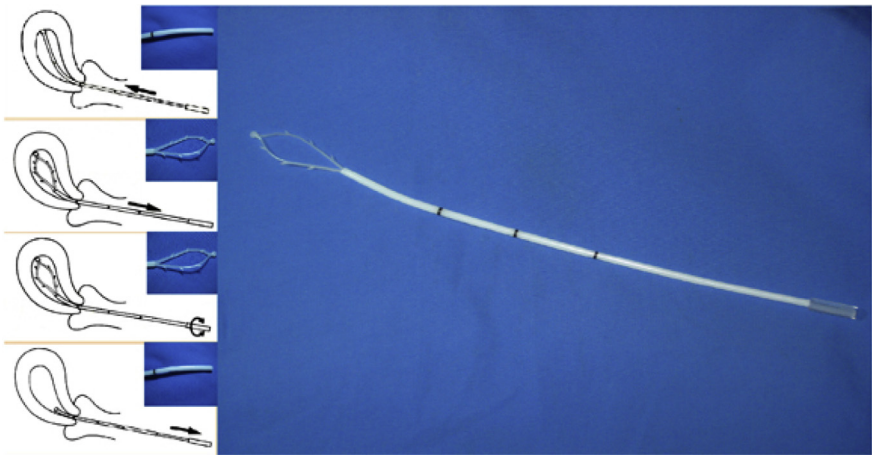

Figure 1. The SAP-1 device.

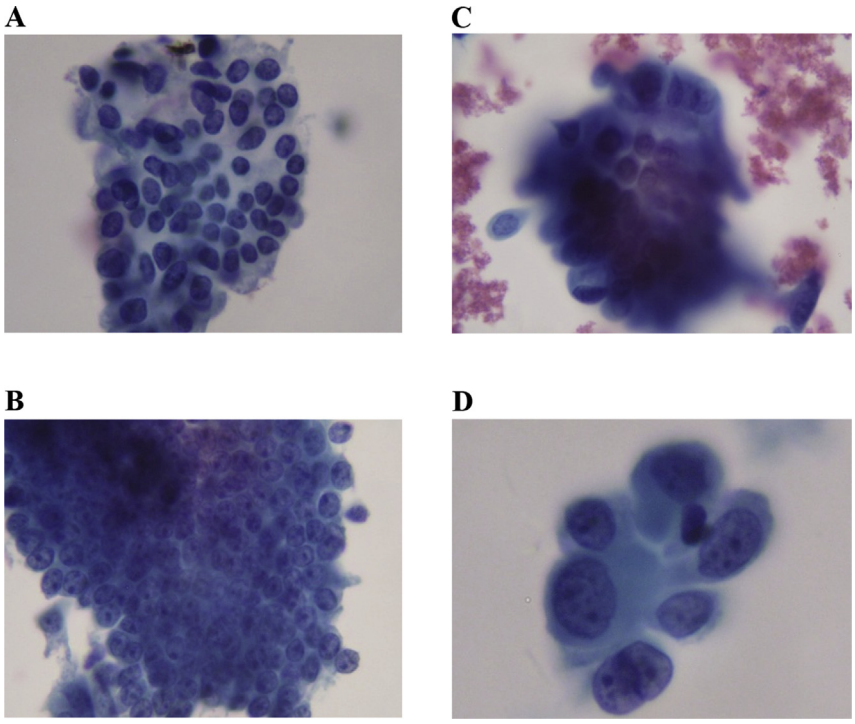

Figure 2. Liquid-based endometrial cytology (Papanicolaou stain; original magnification ×100). (A) Normal endometrium: regularly arranged and monolayer endometrial cells with an oval or round nucleus. The spaces between nuclei are regular, and the chromatin in endometrial cells is delicate. (B) Benign endometrial abnormality: crowded cells arranged into a single layer with delicate chromatin and a small nucleolus. (C) Atypical hyperplasia cell: the spaces in atypical endometrial cells are heterogeneous. Some areas are crowded or even overlapping. The chromatin is coarse. (D) Suspected endometrial carcinoma: variable size cells with obviously round nucleoli. The nucleus to cytoplasm ratio is increasing. Varying and large vacuoles appear inside the cytoplasm.

biopsies), specificity (true negative/all negative biopsies), the PPV (true positive/all positive cytology results), the negative predictive value (NPV; true negative/all negative cytology results); and diagnostic accuracy (true positive plus true negative/true and false positive plus true and false negative). The χ^2 test was used to compare the number of unsatisfactory cytological specimens with that of endometrial biopsies. Statistical significance was judged as $p < 0.05$.

Results

Of the 790 cases, 32 cytologies (4.1%) and 204 curettages (25.8%) were inadequate; and in 13 (1.6%) cases both the cytology and the curettage were inadequate. Of the 204 unsatisfactory endometrial curettages, 110 (53.9%) cases were considered inadequate by the gynecologists because of the scarcity of the sampled tissue, and no endometrial tissue was sent to the pathologists; the other 94 (46.1%) cases were considered inadequate by pathologists in histopathological evaluation.

As indicated in Table 2, Of the 228 postmenopausal women with endometrium < 5 mm, 223 cytologies (96.0%) and 95 curettages (41.7%) were adequate. Of the 562 postmenopausal women with thickened endometrium (≥ 5 mm), 535 cytologies (95.2%) and 491 curettages (87.4%) were adequate. SAP-1 can provide more sufficient material for cytology than D&C can for histology in postmenopausal women ($p < 0.001$).

Table 2
Adequate and inadequate specimens obtained using cytology or dilatation and curettage (D&C).

	Adequate (%)	Inadequate (%)	χ^2	p
Endometrium < 5 mm ($n = 228$)				
Cytology	223 (97.8)	5 (2.2)	170.25	<0.0001
D&C	95 (41.7)	133 (58.3)		
Endometrium ≥ 5 mm ($n = 562$)				
Cytology	535 (95.2)	27 (4.8)	21.64	<0.0001
D&C	491 (87.4)	71 (12.6)		

Potential cytohistological correlation was observed in the remaining 567 cases (71.8%). Detailed analysis of correlation between cytological results and histological diagnosis is presented in Table 3.

Among the 240 cases of normal endometrium diagnosed by cytology, 120 cases were confirmed by D&C: 107 cases were diagnosed as benign endometrial abnormality; five as atypical endometrial hyperplasia; and eight as endometrial carcinoma by D&C. Among the 151 cases of benign endometrial abnormality diagnosed by cytology, 77 were confirmed by D&C: 54 were diagnosed as normal endometrium; five were diagnosed as atypical hyperplasia; and 15 as carcinoma. Among the 96 cases of atypical hyperplasia, 11 were confirmed by D&C: 22 were diagnosed as normal endometrium; 39 as benign endometrial abnormality; and 24 as carcinoma. Among the 80 cases of suspected carcinoma diagnosed by cytology, 66 were confirmed by D&C: three were diagnosed as normal endometrium; eight as benign endometrial abnormality; and three as atypical hyperplasia.

Taking atypical hyperplasia and endometrial carcinoma as a positive result, the diagnostic accuracy of liquid-based endometrial cytology was 81.5%, sensitivity was estimated at 75.9%, specificity at 83.3%, PPV at 59.1%, and NPV at 91.6%.

Discussion

Endometrial carcinoma is the most prevalent gynecological malignancy in developed countries and in developed cities such as

Table 3
Correlation between histologic and cytologic results.

Cytology	Histology (%)				
	Normal endometrium	Benign endometrial abnormality	Atypical hyperplasia	Endometrial carcinoma	Total
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Normal endometrium	120 (21.2)	107 (18.9)	5 (0.9)	8 (1.4)	240 (42.3)
Benign endometrial abnormality	54 (9.5)	77 (13.6)	5 (0.9)	15 (2.6)	151 (26.6)
Atypical hyperplasia cell	22 (3.9)	39 (6.9)	11 (1.9)	24 (4.2)	96 (16.9)
Suspected endometrial carcinoma	3 (0.5)	8 (1.4)	3 (0.5)	66 (11.6)	80 (14.1)
Total	199 (35.1)	231 (40.7)	24 (4.2)	113 (19.9)	567 (100.0)

Beijing and Shanghai in China [1,13]. Early detection plays a critical role in its treatment and survival rate. Currently, the routine diagnostic procedure for patients with postmenopausal bleeding are TVS and D&C. TVS is a noninvasive method but its diagnostic accuracy is debatable. Also, because of the high false-positive rate, TVS does not provide a confirmative diagnosis [14,15]. D&C is an invasive procedure and originally it was intended to serve as a screening tool, but the specimen adequacy was unsatisfactory [16]. Moreover, most patients complained of severe discomfort during the operation and persistent vaginal bleeding after the procedure [17]. Also, this procedure is not easily performed in asymptomatic women.

Traditional endometrial smears are not widely accepted as a diagnostic tool because of their low diagnostic accuracy. In spite of this, in Japan, traditional endometrial cytology has become a routine initial scanning method for endometrial cancer since 1987 [18]. Endometrial cytology has been reevaluated as a diagnostic tool since the adoption of liquid-based cytology techniques. This method overcomes many obstacles, such as distributing cells on a thin layer, and obtaining multiple slides for further analysis [19].

Recent studies emphasized the potential of endometrial thin-layer cytology as the diagnostic tool of endometrial disorders. In 2003, Garcia et al [5] carried out endometrial thin-layer cytology in 203 symptomatic patients and reported a specificity of 96% and sensitivity of 78% with an inadequate rate of 15% (lower than endometrial biopsy, which is 26%). In the same year, Buccoliero et al [20] performed a cytohistology study with concordance of 98%, and an inadequate rate of 18% in a population of 162 women. In 2007, Buccoliero et al [21] performed liquid-based endometrial cytology in 917 premenopausal and postmenopausal women. The authors made a cytohistological correlation analysis, and reported that, in comparison with biopsy, endometrial cytology was more likely to provide sufficient materials. The sensitivity was estimated at 96%, specificity at 98%, PPV at 86%, and NPV at 99%. In the same year, Buccoliero et al [22] performed liquid-based endometrial cytology in a population of 320 asymptomatic women and reported a sensitivity at 94%, specificity at 95%, PPV at 80% and NPV at 99%. The cytological sample was adequate more often than endometrial biopsy [22]. In 2012, Yanoh et al [23] proposed a descriptive reporting format for endometrial cytological diagnosis. They evaluated the sensitivity and specificity of endometrial cytology in 8436 cases from 13 different hospitals. The sensitivity, specificity, PPV, and NPV for detecting atypical endometrial hyperplasia or malignant tumors were 79.0%, 99.7%, 92.9%, and 98.9%, respectively.

The purpose of this study was to evaluate the diagnostic accuracy of endometrial cytology using the SAP-1 device with SurePath preparation. The SAP-1 device was selected due to its ease of use and its small diameter, which makes the procedure painless and convenient, especially for postmenopausal women with cervical stenosis. In addition, it collects endometrial material without cervical contamination. Using this device, the inadequate endometrial sampling rate was 4.1% in the postmenopausal women, which was significantly lower than the D&C (25.8%). It results in higher success rate in collecting cytology specimens compared to histology specimen, particularly in postmenopausal women with endometrium < 5 mm ($p < 0.001$). According to our results, the diagnostic accuracy of liquid-based endometrial cytology was at 81.5%, sensitivity at 75.9%, specificity at 83.3%, PPV at 59.1%, and NPV at 91.6%. It is important to underline that 58.3% (14/24) of atypical hyperplasia diagnosed by histopathology had positive cytological results, and the rate for endometrial carcinoma was 79.6% (90/113). Among the 391 patients with negative cytological results, 358 (91.6%) were confirmed by histopathology.

An improvement to liquid-based cytology could be immunocytochemical analysis. Norimatsu et al [24] reported that a combination of immunocytochemical analysis of PTEN, p53, and β-catenin, in addition to cytomorphologic tests could provide more accurate diagnosis of endometrial cancer in endometrial cytology. Nevertheless, further studies are required to assess the diagnostic accuracy of immunocytochemistry methods, before they can be used as standard diagnostic tools.

In conclusion, our results demonstrate the possibility of liquid-based endometrial cytology as a useful diagnostic tool. The NPV is high enough to exclude endometrial carcinoma or precancerous disease. The SAP-1 device combined with SurePath preparation may become a reliable method for screening endometrial carcinoma in postmenopausal women.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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