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Direct uterine sampling using the SAP-1 sampler device to detect endometrial lesions during histopathological examination

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Summary

Aims: To evaluate the sampling adequacy and diagnostic accuracy of the endometrial SAP-1 sampling device in detecting endometrial lesions based on histopathological examination. *Materials and Methods:* In total, 182 patients who required an endometrial biopsy were enrolled in this study. All of the patients underwent endometrial biopsies with the SAP-1 sampler prior to hysteroscopy (169/182) or dilatation and curettage (D&C) (13/182). Endometrial tissues were obtained at biopsy for histopathological examination. *Results:* Adequate endometrial specimens were obtained in 148 of 182 patients (81.32%). Menopause (p = 0.000), endometrial thickness (p = 0.004), and the types of endometrial diseases (p = 0.009) differed significantly between the two groups. Among the 169 patients who underwent hysteroscopy, sampling scratches were observed in the uterine cavity in 147 cases (86.98%). Compared to traditional methods, such as hysteroscopy and D&C, the sampling diagnostic sensitivity, specificity, and positive and negative predictive values were 82.35%, 100%, 100% , and 97.76% for endometrial carcinoma (n=17) and 37.5%, 100%, 100% and 97.76% for endometrial atypical hyperplasia (n=8), respectively. Those that were misdiagnosed occurred because the lesions were focal or localized in a small part of the uterine cavity. The sampling diagnostic sensitivity for polyps (n=32) was 12.5%. Two patients with submucosal leiomyoma went undiagnosed based on the sample specimens. *Conclusion:* Endometrial sampling using the SAP-1 sampler is a minimally invasive alternative technique for obtaining adequate endometrial specimens for histopathological examination. The SAP-1 sampler was useful in detecting endometrial carcinoma and atypical hyperplasia cases that were not highly suspected to be localized; however, this method was not useful in detecting endometrial polyps and submucosal leiomyomas.

Key words: Endometrial sampling; Endometrial carcinoma; Endometrial atypical hyperplasia; Screening; Endometrial lesions.

Introduction

Endometrial carcinoma is one of the most common types of malignant tumors in the female reproductive system. In the United States, 43,470 new cases occurred in 2010 and 47,130 cases in 2012, but in 2013, the number of new cases increased to 49,560 [1]. In China, as economic development improved, the prevalence of endometrial cancer increased. In Beijing, Shanghai, and Zhongshan, the morbidity rate of endometrial cancer has exceeded that of cervical cancer, thus becoming the most common invasive malignancy of the female genital tract [2]. The screening algorithms for cervical cancer continue to improve; however, the use of cytology techniques to screen for endometrial cancer remains widely unaccepted by the medical community. Directly sampled endometrial cytology specimens can be difficult to evaluate because of hormone-associated morphological changes that occur during the menstrual cycle or because of changes that result from hormonal therapy [3]. Traditionally, endometrial specimens for histological analysis can be obtained through dilation and curettage (D&C) or hysteroscopy, and these methods are considered to be reliable for evaluating the endometrial condition. In the present study, the authors obtained endometrial micro-tissues using the SAP-1 sampler, and they assessed the sampling adequacy of this device to determine whether this approach should be used to detect endometrial lesions.

Materials and Methods

This study was performed from April 2012 to February 2014 at the Obstetrics and Gynecology Department of Peking University People's Hospital. The study was approved by the hospital ethics committee. All of the study participants required endometrial biopsies for indications that included irregular vaginal bleeding, thickened endometrium (assessed by ultrasound, cut-off at five mm without hormonal replacement therapy), abnormal endometrium assessed by ultrasound (i.e., occupational disease of the uterine cavity or heterogeneous), and extrinsically high estrogen levels due to hormone replacement therapy or postoperative tamoxifen use in breast cancer patients with abnormal endometrium assessed by ultrasound. Patients with the following conditions were excluded from the study: (1) a large volume of active vaginal bleeding, (2) confirmed cervical cancer, (3) inability to participate in the study because of severe systemic complications, (4) acute vaginitis or acute pelvic infection, and (5) previous operative hysteroscopy, and (6) adnexal pathology at ultrasound.

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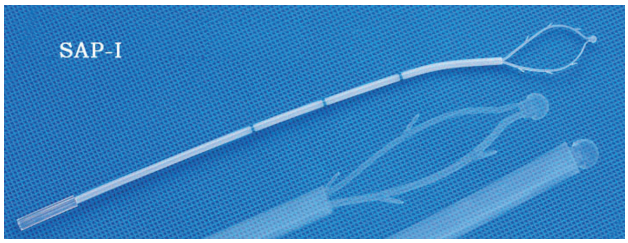

Figure 1. — The SAP-1 sampler device.

Overall, 182 women who were suspected of having endometrial disease according to their local gynecologists were enrolled in this study. After pelvic examination and transvaginal ultrasonography, endometrial sampling via SAP-1 samplers, D&C or hysteroscopy was performed (in this order) in each patient, and the patients whose final pathological results were endometrial malignancy or atypical hyperplasia(n=26) all received hysterectomy.

The SAP-1 sampler device (Figure 1) was patented, and the present hospital in China obtained permission to use this device. While sampling the authors retracted loop sampler completely into the out sheath and gently inserted the device to the level of the fundus. Then they retracted the outer sheath all the way to the handle and rotated the loop clockwise or anticlockwise for 10-15 circles. After having collected the endometrial tissues, they pushed the outer sheath to the tip, removed the device, and immersed the loop with the specimen in neutral buffered formalin. The tissue specimens were embedded in paraffin and stained with hematoxylin and eosin for histopathological examination. The presence of flocculent tissue fragments in the fixed buffer and sufficient material for a histopathological diagnosis indicated that the samples were adequate. After sampling, 169 patients underwent hysteroscopy and 13 patients underwent D&C. During hysteroscopy, it was determined if the sampling scratches from the SAP-1 sampler covered the uterine cavity walls. In addition, endometrial tissues were obtained during the procedure and sent to the pathology department. Two gynecological pathologists who were blinded to the study procedures independently assessed the slides based on World Health Organization diagnostic criteria.

A binary logistic regression analysis and the chi-squared and Fisher's exact tests were used as appropriate. All of the statistical analyses were performed using SPSS software (version 19.0), and a p-value < 0.05 was considered statistically significant.

Results

The following patient characteristics were evaluated and shown in Table 1: age, menstrual status, symptoms and signs, vaginal bleeding while sampling, endometrial diseases, and status of the endometrium. The endometrial thickness cut-off for B-mode ultrasound was 1-45 mm (average, 80 ± 6.33 mm). Among the 182 patients, 115 had abnormal uterine bleeding or vaginal drainage and 121 were described as having a large uterine cavity. Compared to obvious abdominal pain during D&C or after hysteroscopy, all the 182 patients just felt slight discomfort while sampling by using SAP-1 sampler.

Overall, 81.32% of the patients (148/182) had adequate sampling specimens for pathological examination. Age (p = 0.451), status of the endometrium (p = 0.997), vaginal bleeding while sampling (p = 0.094), and uterine position (p = 0.401) did not influence the sampling, whereas menopause, the type of endometrial disease, and endometrial thickness significantly influenced the adequacy of the sampling (Table 2).

In order to evaluate the influences of different endometrial thickness to sampling adequacy, the authors calculated the sensitivity and specificity of the SAP-1 device using different endometrial thickness cut-off values (de-

Table 1. — *Patient characteristics.*

Characteristics	Sampling specimens n=182 (%)
Age	
< 40 years	57 (31.3)
≥ 40 years	125 (68.7)
Menstrual status	
Premenopausal	122 (67.0)
Postmenopausal	60 (33.0)
Uterine position	
Retroposition	36 (19.8)
Mid-position	6 (3.3)
Anteposition	140 (76.9)
Abnormal endometrium assessed by ultrasound	
Occupational disease or heterogeneous	127 (69.8)
Thickness ≥ 5 mm (postmenopausal endometrial)	5 (2.7)
Thickness ≥ 5 mm (postoperative breast cancer patients)	7 (3.8)
Thickness < 5 mm	43(23.6)
Vaginal bleeding while sampling	
Small amount	59 (32.4)
Almost none	123 (67.6)
Endometrial diseases	
Uterine polyps and submucosal myoma & IUD	63 (34.6)
Endometrial carcinoma and atypical hyperplasia	26 (14.3)
Others†	93 (51.1)
Status of endometrium	
Atrophy	58 (31.9)
Hyperplasia	83 (45.6)
Normal	41 (22.5)

† Normal endometrium or benign changes, excluding uterine polyps and submucosal myoma.

Table 2. — *Factors influencing endometrial sampling (results of the last binary logistic regression analysis).*

Step	B	S.E.	Wald	df	p	Exp (B)
Menopause	2.240	0.536	17.456	1	0.000	9.392
Type of endometrial disease			9.376	2	0.009	
Others†	-2.125	1.173	3.280	1	0.070	0.119
Uterine polyps and submucosal myoma and IUD	-3.092	1.132	7.459	1	0.006	0.045
Thickness of endometrium	1.986	0.695	8.155	1	0.004	7.284
Constant	1.541	1.083	2.023	1	0.155	4.668

† Normal endometrium or benign changes, excluding uterine polyps and submucosal myoma.

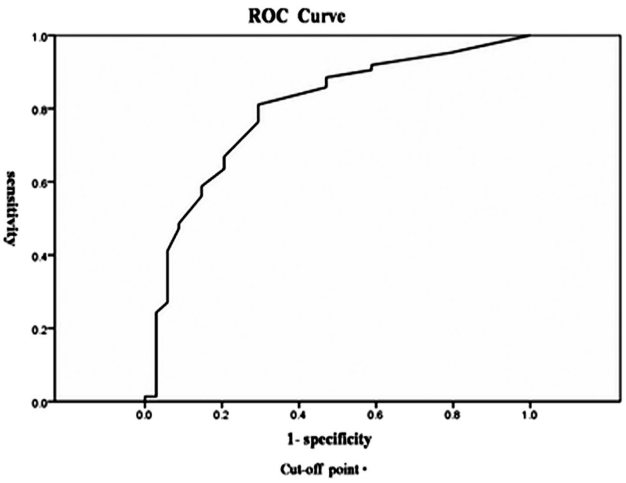

Figure 2. — ROC curve showing the sampling adequacy according to endometrial thickness.

termined by ultrasound) for the threshold and plotted receiver operating characteristic (ROC) curves (Figure 2). The area under the ROC curve was 0.797. Respectively, the cut-offs were defined as four, five, and six mm to obtain the sensitivities and specificities listed in Table 3, and when the cut-off was five mm, the sum of the sensitivity and specificity reached the maximum level (as shown in Table 3). Therefore, the authors set five mm as the cut-off to divide the cases into two groups: < five mm and ≥ five mm. The sampling adequacy was significantly different between the two groups (p = 0.000). The sampling adequacy according to menstrual status and the type of endometrial disease are shown in Table 4.

During hysteroscopy, the authors observed that 86.98% (147/169) of the patients had sampling scratches throughout the uterine cavity during hysteroscopy. The samples of 22 patients (13.02%) were deemed insufficient. In 12 of these patients, scratches were not observed around the opening of the fallopian tube. In eight patients, scratches were only observed in part of the uterine cavity, and in the other two patients, the cavity was not entered because of cervical stenosis, which was detected at the beginning of the study.

Table 3. — *Sensitivities and specificities corresponding to different endometrial thickness measurements.*

Cut-off for endometrial thickness (mm)	Sensitivity	Specificity
4.0	0.6115	0.8235
5.0	0.7165	0.7500
6.0	0.8345	0.6175

Among the 148 patients with adequate sampling specimens, 104 patients (70.27%) received the same pathological diagnosis based on sampling as that based on surgical pathological results (i.e., 17 patients were diagnosed with endometrial carcinoma and eight patients were diagnosed with endometrial atypical hyperplasia). In contrast, using endometrial sampling, three cases (37.5%) of endometrial atypical hyperplasia were detected and 14 cases (82.35%) of endometrial carcinoma were detected, including 12 cases of endometrioid carcinoma, one case of uterine serous adenocarcinoma, and one case of clear cell carcinoma. Compared to traditional methods (hysteroscopy and D&C), the sampling diagnostic sensitivity, specificity, and positive and negative predictive values were 82.35%, 100%, 100%, and 97.76% for endometrial carcinoma (n=17) and 37.5%, 100%, 100%, and 97.76% for endometrial atypical hyperplasia (n=8), respectively. Three patients with endometrial carcinoma were misdiagnosed based on sampling specimens. These 25 patients all undergoing hysterectomy, after the operations the authors found that two of these patients had endometrial lesions localized in a small part of the uterine cavity and were misdiagnosed with endometrial atypical hyperplasia. Additionally, one patient with persistent postmenopausal bleeding in conjunction with uterine enlargement and leiomyoma was misdiagnosed with endometrial benign hyperplasia. Five patients with endometrial focal atypical hyperplasia were misdiagnosed based on sampling specimens: four patients were misdiagnosed with benign hyperplasia and one patient with endometritis. The pathological manifestations of the sampled and surgical specimens of en-

Table 4. — *The sampling adequacy rates for each group*

Groups	Satisfactory sampling % (n)	Unsatisfactory sampling % (n)	p-value
Menstrual status			0.000
Premenopause (n=122)	94.3% (115/122)	5.7% (7/122)	
Postmenopause (n=60)	55.0% (33/60)	45.0% (27/60)	
Type of endometrial disease			0.009
Polyps and submucosal myoma and IUDs (n=63)	58.7% (37/63)	41.3% (26/63)	
Atypical endometrial hyperplasia and carcinoma (n=26)	96.2% (25/26)	3.8% (1/26)	
Others† (n=93)	92.5% (86/93)	7.5% (7/93)	

† Normal endometrium or benign changes, excluding uterine polyps and submucosal myoma.

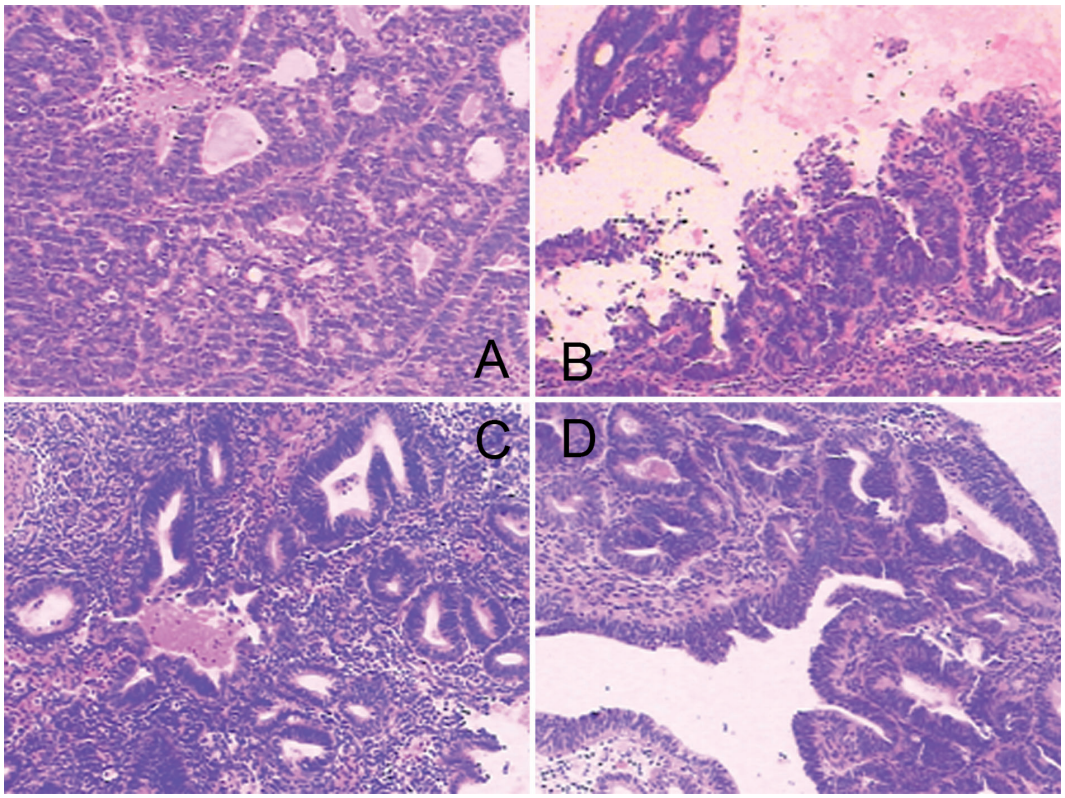

Figure 3. — Endometrial carcinoma (A, B) and endometrial atypical hyperplasia (C, D) ×100 (A, C by surgery; B, D by SAP-1).

dometrial atypical hyperplasia and endometrial carcinoma are shown in Figure 3.

The sampling diagnostic sensitivity, specificity, and positive and negative predictive values for endometrial polyps (n=32) using the SAP-1 sampler were 12.5%, 100%, 100%, and 80.56%, respectively. Two patients with submucosal myoma were not diagnosed based on the sampled specimens.

Discussion

Endometrial cancer is the fourth most common malignancy in women and the most frequent gynecological cancer in developed countries [4, 5]. However, no reliable screening test is available for the early detection of endometrial cancer. Most women with endometrial cancer are diagnosed at an early stage because vaginal bleeding is an early, albeit nonspecific, presenting symptom [6]. The early presenting symptoms and the good prognosis of the majority of endometrial adenocarcinoma cases may explain the limited interest in screening for this neoplasm despite its high frequency and morphological precursors [7].

Currently, endometrial pathology can be identified using several methods, such as transvaginal ultrasound with or without color Doppler and 3-D analysis, hysteroscopy and endometrial biopsies, sonohysterography, and the detection of endometrial cells in cervical cytology slides [8-11]. Transvaginal ultrasound is the most commonly used first-line diagnostic method because it is well tolerated, but the accuracy of this method is based solely on endometrial thickness [10, 11]. Hysteroscopy with biopsy is a second-line diagnostic tool and is considered the gold standard in endometrial pathology detection [12]. However, hysteroscopy requires hospitalization, anesthesia, and an operating room. Recently, endometrial cytology has been evaluated with the introduction of liquid-based techniques that reduce obscuring factors, thereby increasing the diagnostic accuracy [13]. However, endometrial cytology is difficult to evaluate because of hormone-associated morphological changes and well-differentiated adenocarcinoma. Similar to endometrial hyperplasia, endometrial cytology can be characterized by the presence of good cellular cohesion and mild atypia. In addition, approximately 10% of endometrial samples do not provide adequate smears [14], and no worldwide diagnostic standards are available, such as cervical cytology diagnostic criteria. In the present study, the authors directly performed histopathological examinations of sampled endometrial tissue. Several studies have indicated that the Pipelle device was the most accurate device for office endometrial sampling compared with other devices or methods [15]; however, this approach is expensive, so the authors selected the SAP-1 sampler which is produced in China and can also be used to obtain endometrial specimens [16].

In the present study, adequate endometrial samples were obtained from 81.32% (148/182) of the patients using the SAP-1 sampler. This rate is similar to the cytological test rate (approximately 79.1%−99.6%) but lower than the D&C rate (91.8%−99%) [16]. These results may be attributed to the material used in the loop of the SAP-1 device, which was not as hard as the curette. Additionally, the tissues were fragmentized and not sufficient for pathological diagnoses. Overall, 34.6% (64/182) of the patients had uterine polyps, submucosal myoma or IUDs, which can obscure part of the uterine cavity and prevent accurate sampling.

Studies have demonstrated that the percentage of the endometrial surface area sampled by the Pipelle device is approximately 5% [17]. In the present study, during hysteroscopy, approximately 86.98% (147/169) of the patients had sampling scratches throughout the uterine cavity. Therefore, by using SAP-1 devices, the present authors were able to biopsy most of the uterine cavity.

The present authors found that menopause status, the types of endometrial diseases, and endometrial thickness significantly influenced the sampling accuracy of the SAP-1. Elsandabesee and Greenwood [18] estimated that there was a 27% probability of obtaining an adequate endometrial sample from women with thin endometrium, and the ability to obtain an adequate endometrial sample using the Pipelle device can be adversely affected by an endometrial thickness less than five mm. In the present study, the authors found that with an endometrial thickness cut-off value that ranging from four to six mm, the sensitivity increased from 61.15% to 83.45%, whereas the specificity decreased from 82.35% to 61.75%. When the cut-off was five mm, the sum of the sensitivity and specificity reached the maximum level. Usually, when endometrial thickening is detected by ultrasound, office hysteroscopy with endometrial biopsy is indicated, which is considered the gold standard. Nevertheless, these procedures are not well tolerated despite the introduction of mini-hysteroscopes and flexible hysteroscopes, which have reduced the discomfort produced by traditional hysteroscopy [19, 20]. In the present study, the histological sampling was well tolerated by all patients, and no complications were observed. Therefore, when the endometrial thickness cut-off is greater than five mm, the SAP-1 sampler can be utilized to biopsy the endometrium. However, when the cut-off is less than five mm, traditional methods are preferred, such as D&C or hysteroscopy.

The number of unsatisfactory samples from patients with uterine polyps has been reported to be as high as 54% with endometrial aspiration biopsy. Among these unsatisfactory samples, 20% are found to have a type of pathology upon subsequent investigation [21]. In addition, it can be difficult to diagnose polyps and leiomyoma from sampling specimens. Iavazzo *et al.* [22] found that the sensitivity, specificity, and positive and negative predictive values for endometrial polyps by sampling were 14.7%, 100%, 100%, and 69.5%, respectively. In the present study, the diagnostic sensitivities for endometrial polyps and submucosal myoma using the SAP-1 sampler were 12.5% (4/32) and 0% (0/3), respectively. Therefore, if patients are highly suspected of having uterine polyps or submucosal myoma, it is more suitable to obtain their endometrial samples using traditional methods.

False-negative results may occur when tumors are localized to a polyp or a small surface area of the endometrium [23]. Bakour *et al.* [24] affirmed that in cases with focal lesions, only minimal tissue can be obtained. Additionally, Iavazzo *et al.* [22] found that the detection of endometrial pathology using the Uterobrush depends on the size and type of the lesion and on its location in the uterine cavity. Similarly, curettage has a poor detection rate for focal lesions, with reported failure rates ranging from 38% to 100% [25]. In the present study, the authors identified three patients with endometrial cancer based on their surgical specimens, despite having negative preoperative endometrial samples. Two of these patients had endometrial lesions localized in a small part of the uterine cavity, with one patient experiencing persistent postmenopausal bleeding in conjunction with uterine enlargement and leiomyoma. Five patients with atypical endometrial hyperplasia were misdiagnosed based on their sampling specimens because the lesions were focal or polypoid; therefore, it was difficult to obtain proper specimens from the SAP-1 sampler. Thus, if a patient is highly suspected of having an endometrial malignancy but her ultrasound or MRI results show that the lesions are localized, hysteroscopy should be used for further analysis. Otherwise, the SAP-1 device should be selected due to its simple operation, good tolerance, and minimal invasiveness, and accurate histopathological results can be obtained from micro-tissue samples. Finally, when gynecologists and pathologists are more familiar with this method, the results should improve.

The SAP-1 sampler is a minimally invasive alternative technique used to obtain an adequate endometrial sample for histopathological examination, with high sensitivity and specificity for detecting malignancy. The use of the SAP-1 sampler for endometrial sampling in patients with abnormal uterine bleeding and an endometrial thickness greater than five mm could obviate hysteroscopy or D&C. However, if patients are highly suspected of having polyps or leiomyoma, the lesions are localized in the uterine cavity or a focal malignancy is present, hysteroscopy should be used to obtain endometrial specimens. Future studies with larger patient cohorts that assess the role of endometrial sampling in the detection of lesions are necessary to better familiarize gynecologists and pathologists with this method.

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