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The application of endometrial sampler SAP-1 to screening of endometrial cancer in postmenopausal women: A diagnostic test study

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Abstract
With cytology for screening cervical cancer providing a successful reference, endometrial cancer screening has attracted more attentions recently. The objective of this study is to evaluate the application of endometrial sampler SAP-1 as a screening tool to detect endometrial cancer among postmenopausal women. From August 2018 to February 2021, 54 postmenopausal women were hospitalized for undergoing hysteroscopy examination. Before the procedure, endometrial samples were collected by the method of SAP-1. The histological results were compared with those by hysteroscopy sampling. The satisfactory rate for the endometrial specimen by SAP-1 sampling was 88.9%. The sensitivity, specificity and accuracy rate of SAP-1 sampling for diagnosing the cancer or precancerous lesions of endometrium were 87.5%, 100% and 97.9%, respectively. Among these patients, whether they had bleeding symptoms, endometrial thickening or intrauterine occupying lesions, risk factors for endometrial cancer or not, the diagnostic coincidence rate of SAP-1 sampling was over 96%, and the differences were not statistically significant (P>0.05). In conclusions, in postmenopausal women, SAP-1 sampling is an ideal screening method, regardless of whether the patients have bleeding symptoms, endometrial thickening or intrauterine occupying lesions, endometrial cancer risk factors. The diagnostic coincidence rate is quite high, but it still needs large sample study to verify.

Keywords: Endometrial sampler, postmenopausal women, endometrial cancer, screening

Introduction
In recent years, endometrial cancer (EC) has been the most prevalent gynecological malignancy in some developed countries, as well, in some developed cities in China [1-2]. Despite the incidence of EC presents a younger trend, the postmenopausal women still account for the majority group of EC sufferers [3]. Among them, postmenopausal bleeding and endometrium thickening (>5mm) are the most common indications for EC screening. For suspicious patients, the current gold standard of diagnosis is based on histopathological examination of endometrium obtained by dilatation and curettage (D & C) with hysteroscopy assistance, which enable the direct visualization of the uterine cavity and targeted biopsy. However, the procedure is invasive, high cost, requiring complicated manipulatory techniques, and has the risk of complications such as uterine perforation, making it not suitable as a screening method for wide clinical practice.

Being a non-invasive approach, trans-vaginal ultrasound (TVU) is commonly recommended as the first-line endometrial evaluating method, but the accuracy seems to be based solely on endometrial thickness (ET) [4]. In some studies, some other ultrasound indicators, such as endometrial morphology, endometrial-myometrial junction regularity and Doppler velocimetry of the uterine arteries, had been reported to improve the predictive value of TVU for detecting EC, while results from other studies are conflicting [5]. In addition, the procedure is operator dependent, and the different ET cut-offs also affect its clinical utility [6]. Besides TVU, the search for circulating biomarkers to facilitate the early detection of cancer has gained great momentum over the last decade, showing the potential of some blood test techniques at differentiating early stage EC cases from healthy controls, while requiring further verifying [7-10]. Until now, there are no consensus on protocols for EC screening. In the past decades, research on the early detection of EC has been focusing on minimally invasive histopathologic and cytopathologic procedures. Therefore, various endometrial samplers have been designed according to different mechanisms, mainly aspirating and scratching.

In most studies, endometrial sampling were shown to be low-risk, cost-effective, and having both high specimen satisfaction and diagnostic accuracy including sensitivity and specificity. Due to the outstanding feature mentioned above, endometrial sampling has been suggested to be used as the first step for diagnosing EC in some guidelines [11-13]. In the newly published recommendations for protocol in screening EC composed by Chinese experts [14], micro histopathological examination of endometrium by method of sampler is an effective way for screening and early diagnosis of EC.

Sampler Li brush and SAP-1, both designed by Chinese scholars, have been experimented in the attempt to screen EC since their patents issued in the past few years. The results seem inspiring while the data are quite limited when compared with sampling devices, such as Pipelle and Tao brush, commonly used in other countries. SAP-1 was formally initiated in our hospital in August, 2018.

Aims and Objectives

To explore the role of SAP-1 in EC screening among postmenopausal women who underwent hysteroscopy evaluation, by comparing the endometrial pathologic results by method of endometrial sampling and hysteroscopic D&C or electrocision.

Materials and Methods

This prospective study was performed in the Obstetrics and Gynecology Department of Kiang Wu Hospital, Macao Special Administrative Region of China. Postmenopausal women who were admitted to hospital for hysteroscopy between August 2018 and February 2021 were enrolled into this trial. The indications included postmenopausal bleeding, atypical glandular cells found in TCT, thickened endometrium or intrauterine occupying lesion assessed by transvaginal or transrectal ultrasound. Patients with at least one of the following conditions were excluded: anticoagulation therapy, diagnosed coagulopathy, acute vaginitis or acute pelvic infection, a previous diagnosis of invasive cervical cancer, severe cardiopulmonary insufficiency. The protocol of the study was approved by the ethics committee of Kiang Wu Hospital. All participants were fully consulted, and then signed informed consent. There was no financial interest or any arrangement with the companies producing the instruments used in the study.

The procedure was performed under intravenous anesthesia in operation room. First, the patients were placed in the lithotomy position and sedated with intravenous anesthetics. Then the operator performed a bimanual pelvic examination to identify the size, shape and orientation of the uterus. After the perineum was cleaned and a bivalve speculum was inserted, the vagina and cervix were carefully cleaned. Next, the sampler SAP-1 used in this study is manufactured by Saipujiuzhou Company, Beijing, China. (Fig.1) It measures 3 mm in diameter and 250 mm in length. It consists of a flexible latex loop with burrs 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 or anticlockwise from the upper uterine cavity to underpart for 20-25 circles, thus collecting tissue on the edges of the curette. It was then withdrawn into the sheath and removed out of the uterus, the loop with the specimen was exposed and immersed in the sample container. Last, hysteroscopy was performed using a 5-mm optic with saline solution distension after the endometrial sampling. Histologic sampling was performed by D & C, or electrocision when necessary. Complications from the procedures were also recorded.

The endometrial specimens were collected into two separate containers labeled 'SAP-1 sampling' and 'endometrial curettage', then sent to the Department of Pathology. Endometrial samples were routinely fixed in neutral buffered for mol, embedded in paraffin, and stained with hematoxylin and eosin. Each specimen was examined by the same pathologist to decrease inter observer variability.

The slides were considered unsatisfactory samples when there were severe fragmentation or scarcity of the endometrial tissue without endometrial glands and stroma under the microscope. The endometrial histological criteria used in this study were according to the World Health Organization (WHO) criteria in 2014 [15]. The endometrial pathology was categorized as benign when the histology revealed secretory endometrium, proliferative endometrium, atrophic endometrium, endometritis, non-atypical hyperplasia, endometrial polyp or sub mucous myoma.

Statistical analysis was carried out using SPSS version 20.0 (SPSS, Chicago, IL, USA). The pathology results of SAP-1 sampling were compared with the hysteroscopic pathological results using a double access table. The sensitivity, specificity, diagnostic accuracy (true positive plus true negative/true and false positive plus true and false negative) of SAP-1 sampler in diagnosing endometrial carcinoma and atypical hyperplasia were calculated. Clinical variables were compared using the $\chi 2$-test. The differences were considered significant when the P-value was <0.05.

Results

A total of 54 postmenopausal patients were included in this study. The patients' age ranged from 52 to 74 years (mean 58.6±6.2 years), and they have menopause for 1~24 years (mean 8.2±6.0 years).

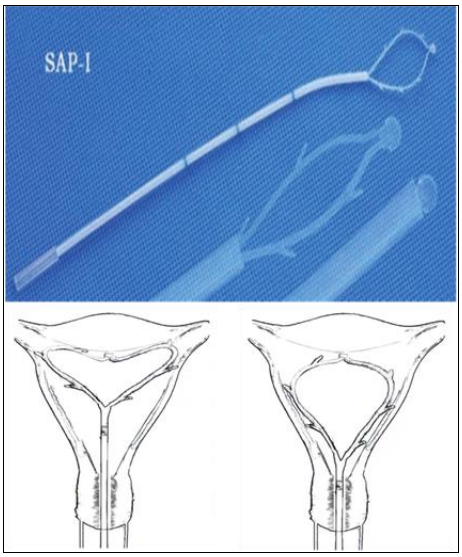

Fig 1: The SAP-1 sampler device

1. The comparison of specimen satisfaction rate between two sampling methods

The satisfaction rate of SAP-1 sampling was 88.9%, which was slightly lower than 96.3% of hysteroscopic D&C or electrocision, but there was no significant difference between the two methods ($P > 0.05$), as indicated in Table 1.

Table 1: Satisfactory and unsatisfactory specimens obtained using two methods

Sampling method	Satisfactory (n)	Unsatisfactory (n)	Satisfactory rate (%)	$\chi 2$	*P*
SAP-1	48	6	88.9	2.16	0.142
Hysteroscopic	52	2	96.3		

2. Pathological results of two methods

In this study, hysteroscopic sampling specimens of 52 patients were considered satisfactory in histopathological evaluation. The pathological results were as follows: 32 cases of menopausal or proliferative endometrium, 4 cases of endometrial polyps, 3 cases of endometritis, 3 cases of sub mucous myoma, 2 case of endometrial complex hyperplasia, 1 case of endometrial atypical hyperplasia, 7 cases of endometrial cancer. The satisfactory pathological results of 48 patients with SAP-1 were as follows: 37 cases of menopausal or proliferative endometrium, 2 cases of endometrial polyps, 2 case of endometritis and 7 cases of endometrial cancer. It is worth noting that, totally, 8 cases including EC and precancerous lesions were found in present study, and 7 EC cases diagnosed by SAP-1 were completely identical with those by hysteroscopic sampling, with none of them missed. But 1 case of endometrial atypical hyperplasia was missed. As shown in Table 2, the diagnostic accuracy of SAP-1 was 97.9% with hysteroscopic pathology as the gold standard, significantly superior to those of endometrial thickness and commonly-used tumor marker.

Table 2: The diagnostic accuracy of EC and precancerous lesion by different methods using hysteroscopic sampling result as a reference

Hysteroscopic sampling	EC/Precancerous lesion					
	SAP-1		Endometrial thickness		Tumor marker(Ca125,HE4)	
	Positive	Negative	≥5mm	<5mm	+*	-^
Positive	7	1	6	2	3	5
Negative	0	40	20	20	5	35
Sensitivity (%)	87.5		75		27	
Specificity (%)	100		50		87.5	
Accuracy (%)	97.9		54.2		79.2	
$\chi 2$			25.2[a]		8.32[a]	
P			0.000001		0.004	

*+: at least one of the serum Ca125 and He4 elevated beyond normal range

^-: both of the serum Ca125 and He4 in normal range

[a]: when compared with SAP-1

3. The accuracy of pathological diagnosis of SAP-1 sampling in patients with different clinical characteristics

48 patients, whose endometrial specimens were both satisfactory by two sampling methods, were classified according to the following clinical features, and the diagnostic coincidence rate of SAP-1 was evaluated.

(1) Bleeding or not: 32 cases with bleeding, 16 cases without bleeding.

(2) According to ultrasound, there were 26 cases of endometrial thickening (≥5mm) or intrauterine occupying lesions, and 22 cases of normal endometrial thickness (< 5mm) and no intrauterine occupying lesions

(3) High risk patients: main risk factors of endometrial cancer according to Chinese recommendation [14]: A. obesity, BMI ≥ 30kg / m2; B. history of polycystic ovary syndrome; C. history of estrogen single use without progesterone; D. late menopause (> 55 years old); e. lifelong infertility or primary infertility; F. long term treatment of tamoxifen (especially for patients > 50 years old or still using tamoxifen after menopause); G. age ≥ 45 years old with diabetes; H. lynch syndrome patient, the third-class family members who have Lynch syndrome but herself has no related gene testing, and the family history of endometrial cancer or colon cancer. Those with at least anyone of the above are at high risk. There were 10 high-risk patients and 38 non high-risk patients in this study.

Table 3: The accuracy of pathological diagnosis of SAP-1 sampling in patients with different clinical characteristics

SAP-1 sampling		Hysteroscopic sampling		Coincidence rate (%)	$\chi 2$	*P*
		Positive	Negative			
Bleeding	Positive*	5	0	96.9	0.511	0.475
	Negative#	1	26			
Non	Positive	2	0	100		
	Negative	0	14			
Endometrial thickening or intrauterine occupying lesions	Positive	5	0	96.2	0.864	0.353
	Negative	1	20			
Non	Positive	2	0	100		
	Negative	0	20			
High risk	Positive	2	0	100	0.269	0.604
	Negative	0	8			
Non	Positive	5	0	97.4		
	Negative	1	32			

* : refers to the pathological result indicating benign status including menopausal or proliferative endometrium, endometritis etc.

: refers to the pathological result indicating EC or atypical hyperplasia

It can be seen from Table 3 that the diagnostic accuracy of SAP-1 sampling in postmenopausal women were all more than 96% regardless of whether they had bleeding symptoms, endometrial thickening or intrauterine occupying lesions, and whether they had risk factors for EC, and the differences were not statistically significant (all $P > 0.05$).

Discussion

In the past few years, EC has surpassed cervical cancer as the leading malignancy of female genital tract in some developed countries and districts [1-2]. As well, the incidence is on the rise year by year, which has been largely attributable to increased obesity epidemic, with longer life expectancy also playing a role [16]. What should be noted is that there has been a relatively complete screening system for cervical cancer. Even though the sensitivity by way of cytology for screening cervical cancer is only 60% to 70%, the widespread utility of this simple method leads to the sharp reduction in the incidence rate of cancer by surprisingly 90% [17, 18]. The incidence trend of these two major female malignant tumors, showing one rising while the other one dropping, demonstrate convincingly that screening plays an important role in disease prevention and control. Similar to the anatomical and biologic behavior characteristics of cervical cancer, EC lesions are mostly confined to the uterine body, and develop slowly, with late metastasis and dissemination, which offers us the opportunity to screen EC within quite a long time. According to the literature, almost half of endometrial atypical hyperplasia, considered as the precancerous lesions of EC, if remained untreated, will develop into cancer in 10 years. Three quarters of EC cases are diagnosed with low stage disease, largely due to abnormal vaginal bleeding being present in 94% of the cases [19]. Five-year overall survival rate ranges from 74% to 91% for FIGO stage I-II, the highest of all gynecological cancers. While diagnosed at a late stage (IV), the survival is poor with only 20-26% of women surviving for 5 years [20]. Therefore, with the cervical cancer cytology screening providing a successful reference, early EC screening is of great clinical and social significance for the diagnosis and treatment of this disease.

However, it should also be recognized that cervical cancer screening has natural advantages over EC screening: the cervix can be viewed directly under the vaginal speculum; sampling is relatively noninvasive or minimally invasive; the process is quite simple, the patient will feel no obvious pain, and there is no need for extra consumption such as anesthesia. EC screening, by contrast, inevitably needs invasive manipulation. Although the standard diagnosis of EC by D&C is strongly supported by modern minimally invasive techniques such as hysteroscopy, it is not suitable for the routine screening process. When compared with some other screening methods, which are indirect and without ideal diagnostic sensitivity and specificity, such as transvaginal ultrasound, serum tumor markers (CA 125, HE 4, *et al.*), direct endometrial pathology still remains the gold standard. Therefore, the core issue of screening is whether the endometrial specimen acquisition method can be both minimally invasive and inexpensive. At present, scholars all over the world have done a lot of research and attempts in this area. Cytopathology, based on endometrial exfoliated cells (ECT), proposes a new idea for the diagnosis of endometrial diseases with its advantages of painlessness, accuracy, easy operation and low cost, but it cannot provide some indispensable information for histological diagnosis, such as endometrial gland morphology, gland and stroma ratio. Furthermore, there is a lack of gold standard agreed by cytologists. Therefore, ECT screening method is still unable to replace histopathological diagnosis, and has not been widely recognized and promoted in this domain [21]. Endometrial samplers, represented by Pipelle and Tao brush, using principle of circular scraping or negative pressure suction to obtain endometrial samples for micro histopathological diagnosis, have recently become a new, simple, safe, painless, high-quality and low-cost screening method [22]. The endometrial sampler SAP-1 used in this study is composed of a ring-shaped burr like structure (6 toothed scraps), which can be used for 360-degree circular curettage to obtain small-amount but enough endometrial tissue samples for pathological diagnosis [23]. The status of ovarian failure and low serum estrogen level in postmenopausal women, leads to endometrial atrophy and thinning, which often, in turn, results in failure of endometrial sampling or insufficient specimens, even in the circumstances of conventional D&C. In this study, the sample satisfaction rate by method of SAP-1 in postmenopausal women was more than 90%, which was consistent with the literature [24], and also similar to other different types of endometrial sampling devices [22].

It was reported that incidence rate of EC increased significantly with age. The onset peak age was 50~59 ys, and the average age of diagnosis was 55 ys, with over 90% occurring in women over 50ys [24, 25]. So, postmenopausal population was the uppermost priority in EC screening. Ma *et al.* [24] carried out an investigation on the diagnostic accuracy of liquid-based endometrial cytology, performed by brushing the uterus cavity using SAP-1, in comparison with histology among 790 postmenopausal women, who scheduled for hysteroscopy. SAP-1 was found to provide more sufficient material for cytology than D&C can for histology. Taking atypical hyperplasia and EC as a positive result, the diagnostic accuracy of liquid-based endometrial cytology was 81.5%. In this study, the coincidence rate of SAP-1 in the diagnosis of EC and precancerous lesions was 97.9% based on the pathological results of hysteroscopic sampling. Among them, 7 cases of EC were completely consistent, with none of them missing diagnosis. One case of endometrial atypical hyperplasia was misdiagnosed, with the lesion located in a small area of an endometrial polyp. The misdiagnosis may result from that SAP-1 can only collect the mucosal tissue on the surface of the uterine cavity, but cannot collect the interstitial or muscular tissue below it. Therefore, SAP-1 is not suitable for the cases of intrauterine occupying lesions such as fibroids and polyps [21]. The result of our study also demonstrated that whether or not postmenopausal women had bleeding symptoms, endometrial thickening or intrauterine occupying lesions, and EC risk factors, the diagnostic coincidence rates of SAP-1 sampling were all more than 96%, suggesting that SAP-1 could be an ideal method for EC screening in postmenopausal women.

Some limitations of this study deserve to be underlined. First, the sample size is quite small, due to the short duration after the initiation of SAP-1 in our hospital, and the limited population size in our region. Second, we cannot evaluate the pain in the endometrial sampling process under anesthesia status. Therefore, the application of SAP-1 in EC screening still needs large sample study to verify.

Conclusion

In conclusion, in postmenopausal women, SAP-1 sampling is an ideal screening method, regardless of whether the patients have bleeding symptoms, endometrial thickening or intrauterine occupying lesions, endometrial cancer risk factors. The diagnostic coincidence rate is quite high, but it still needs large

sample study to verify.

Disclosure
None declared.

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