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Factors affecting adequacy of Pipelle and Tao Brush endometrial sampling

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Objective To compare factors influencing adequacy of endometrial samples obtained using two outpatient sampling devices – Pipelle and Tao Brush.

Design Pragmatic unblinded trial with investigation schedule randomised separately within two groups according to endometrial cancer risk.

Setting Gynaecology outpatient clinic of a large city hospital in Edinburgh, Scotland.

Population All women referred to a gynaecology outpatient clinic during a 28-month period complaining of abnormal vaginal bleeding.

Methods Women were assigned to two 'risk groups' for endometrial cancer ('high risk' for postmenopausal women and 'moderate risk' for premenopausal women aged over 40 years or with other risk factors). Women in each risk group had both types of biopsy and were randomised to two outpatient visualisations: hysteroscopy and/or transvaginal ultrasound scan.

Main outcome measures Completion of the investigation, adequacy of sample and acceptability of investigation to women.

Results In 200 high-risk women, adequate samples were significantly more likely to be obtained by Tao Brush than Pipelle ($P < 0.001$). Nulliparity was strongly associated with failed insertion for both devices ($P < 0.001$). Inadequate samples were strongly associated with postmenopausal status only for Pipelle ($P < 0.001$), and among premenopausal women, for both samplers, with nulliparity ($P < 0.001$). A significantly greater proportion of women preferred the Tao Brush to the Pipelle endometrial sampler ($P < 0.001$).

Conclusions In postmenopausal women, Tao Brush sampling offers advantages over use of Pipelle, and the former should be considered as an alternative or additional sampling device in this group of women.

Keywords Abnormal uterine bleeding, endometrial biopsy, Pipelle, Tao Brush.

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Introduction

Abnormal uterine bleeding (AUB) is a very common presenting complaint to the gynaecologist, but the underlying pathology varies between different groups of women. Abnormal perimenopausal or postmenopausal bleeding (PMB) is associated with endometrial carcinoma in approximately 10% of women,[1] but in menstruating women, excessive menstrual blood loss is not usually a symptom of immediate concern with respect to malignancy. However, there is a range of benign focal lesions, such as fibroids and polyps, that may be responsible for AUB,[2] and evaluation of the uterine cavity is usually required, particularly if irregular blood loss is reported. In groups of women at risk of endometrial cancer, endometrial biopsy is one of the mainstays of clinical investigation, and is usually combined with 'visualisation' by means of hysteroscopy or ultrasound scan. If the endometrial thickness on ultrasound scan is 3 mm or less, sampling is not considered necessary, as the risk of endometrial cancer in this circumstance is very low.[3] Endometrial sampling in the outpatient setting is generally an effective and acceptable method to obtain endometrial samples for histological assessment,[4,5] but around 10% of outpatient endometrial samples do not provide adequate tissue, with inadequate sampling being most problematic in the postmenopausal group in whom up to 68% of endometrial samples are reported to be inadequate.[6]

However, a sample that yields very scanty amounts of tissue can still be reassuring if a postmenopausal woman also has an endometrial thickness of less than 5 mm when measured on ultrasound scan[7] or if hysteroscopy reveals an atrophic endometrium.[8] However, if the endometrial thickness is greater than 5 mm then histological analysis of an endometrial sample is indicated,[7] whereas if the endometrial thickness is between 3 and 5 mm the need for an endometrial sample differs according to the factors applying, whether the woman is postmenopausal or premenopausal[9] (when up to 21.5% of samples are inadequate). In determining the endometrial thickness requiring further investigation, practice varies in the UK between 3 and 5 mm. There is a balance to be struck between sensitivity and specificity – at the lower thickness of 3 mm, fewer cases of endometrial cancer will be missed, but at the cost of referring a much larger number of women for investigation who do not have cancer.[3] Problems of inadequate sampling with Pipelle samplers, particularly in postmenopausal women, have stimulated interest in alternative methods of obtaining an outpatient endometrial sample.

The Tao Brush IUMC endometrial sampler® is an inexpensive disposable sheathed brush device which may be introduced into the endometrial cavity in the outpatient setting without the need for anaesthetic.[10,11] Once inside the uterine cavity, it is unsheathed and rotated to harvest endometrial cells onto the surface of its nylon bristles. After resheathing to prevent contamination by cells from the endocervix and lower genital tract, the brush is removed. The cells are washed from the brush into a preservative fluid, and in the laboratory, a liquid-based cytology (LBC) preparation is made, either by conventional cytocentrifugation or using SurePath or ThinPrep preparation systems. From the residue, it is also possible to prepare a cell block that can yield microbiopsies for histological assessment. Although it requires training of pathologists to interpret the Tao Brush specimen, the method is simple to use, inexpensive and appears well tolerated by women.[12,13] As this sampling technique has not yet been widely adopted, data on sensitivity and specificity are scanty and numbers of women are small, but Tao Brush biopsy is reported to have 100% sensitivity and up to 96% specificity for atypical hyperplasia or endometrial carcinoma.[14,15]

LBC has greatly aided the microscopic assessment of endometrial brush specimens as it eliminates air-drying artefacts and removes the obscuring elements of blood and mucus that tend to hamper direct conventional smear methods. Fluid phase fixation allows the cytological features of individual cells to be assessed, but at the same time, glandular and stromal tissue architectures tend to be at least partly maintained.[16,17] It is, therefore, possible to assess the endometrial sample at almost the same level of detail as conventional histology and accurate dating of the endometrium in the normal menstrual cycle is possible. Endometrial malignancy can be reliably identified and cytological atypia is identifiable if present in hyperplastic lesions. However, it can be more difficult to identify some nonatypical hyperplastic lesions in which the histological diagnosis rests on assessment of architecture of relatively large areas of the endometrium.

The aim of this study was to compare the performance of Pipelle and Tao Brush endometrial samplers, among women with complaint of AUB (who had moderate to high risk of endometrial cancer and had an endometrial biopsy as part of their schedule of investigations), in terms of patient acceptability of procedure and success in obtaining adequate sample for histological examination. Some of the results of the study have been reported in part in a previous publication[12] but the paper presented here provides a detailed comparison of the two sampling devices, and an examination of factors associated with sampler performance.

Methods

Study design and patients

The design of the study has been reported elsewhere.[12] It was designed to compare different methods of endometrial evaluation using a pragmatic randomised study design, including two types of biopsy – Pipelle endometrial sampler (Laboratoire CCD, Paris, France) and the Tao Brush (Cook OB-GYN, Bloomington, IN, USA). As the risk of endometrial cancer differs depending on age, menopausal status and specific risk factors, women were divided into three groups on the basis of risk of endometrial cancer: a high-risk group (postmenopausal), a moderate risk group (premenopausal and aged 40 years or over, or aged under 40 but having known risk factors for endometrial cancer, namely polycystic ovary syndrome, prior use of unopposed estrogens or tamoxifen, obesity, diabetes, or family history of endometrial cancer)[18] and a low-risk group (the remaining premenopausal women). Randomisation to different combinations of outpatient investigations – endometrial biopsy, hysteroscopy and ultrasound scan – was completed separately within these risk groups.

Recruitment to the low-risk group proved difficult, possibly because of changing practice with regard to referral and endometrial investigation in women under 40 years and despite the fact that the study design randomised low-risk women to a generally lower degree of investigation, including a potentially large 'no investigation' arm and where the randomisation was to investigate by biopsy, this involved only one biopsy, either Pipelle or Tao Brush. Therefore, of 157 women recruited to this group, 34 were randomised to Pipelle and 29 to Tao Brush. In contrast, all women in the moderate ($n = 326$) and high-risk ($n = 200$) groups were assigned sampling by both devices (paired design), with order randomised, to ensure unbiased and statistically powerful comparison between the two devices. Furthermore, these groups are most representative of patients likely to need endometrial biopsy. This report will, therefore, be confined to findings for the

high-risk (menopausal) and moderate risk (premenopausal, mostly over 40 years of age) groups (total $n = 526$).

The women were blinded to which device was used first, and after the appointment wherein sampling was undertaken, completed a 'biopsy report' that included a question about their preference between the two biopsy methods experienced – 'first' or 'second'. However, it was not possible to blind the clinicians. All the women were randomised to receive in addition, at least one 'visualisation' procedure: hysteroscopy and/or transvaginal ultrasound (usually in conjunction with abdominal ultrasound and in a small number of cases substituted by abdominal ultrasound). In the high-risk group, 50% had ultrasound and biopsy (U + B) and 50% had hysteroscopy and biopsy (H + B). In the moderate risk group, 25% each had U + B, H + B, H + B + U or B only. For women randomised to hysteroscopy (or both hysteroscopy and ultrasound), both biopsies occurred at the time of the hysteroscopy, after visualisation. In the case of women randomised to ultrasound alone, the biopsy generally occurred at the initial clinic visit with the ultrasound appointment scheduled for another later appointment; since there was a waiting time for ultrasound, it was accepted that for the women randomised to receive U + B, the biopsy should be taken at the initial clinic visit, when a pelvic examination was being undertaken anyway. Although it was recognised that delay may have added to patient anxiety, it was considered unethical to delay biopsy, and in addition it may have affected clinicians' willingness to allow their patients to be recruited.

A total of 526 women were recruited from 767 eligible women attending the Gynaecology Outpatient Department, Royal Infirmary of Edinburgh between January 1999 and May 2001, with a GP referral for the investigation of abnormal vaginal bleeding. Women were recruited only if informed consent was given to participate, and the clinicians in charge of their care agreed to their being randomised. The study included women using oral contraception or hormone replacement therapy (HRT) but excluded those who were pregnant or who had difficulty in reading or writing English.

Biopsy methods

Pipelle endometrial sampling

The Pipelle endometrial sampler obtains a small sample of endometrium for histological assessment without dilatation of the cervix; and as there is usually minimal discomfort associated with the procedure it may be conducted in the outpatient setting. Tissue samples obtained were collected into 10% neutral buffered formalin, routinely processed in the pathology laboratory and embedded in paraffin. About 5-μm tissue sections were cut, mounted, dewaxed and stained with haematoxylin and eosin. The biopsies were routinely reported by consultant pathologists in the Biopsy Service without consultation with the study pathologist (A.R.W.W.).

Tao Brush sampling

The Tao Brush permits sampling of the surface of the endometrium without excessive manipulation and produces a sample uncontaminated by material from the lower genital tract.[11] Cellular material was transferred to a test tube containing CytoRich Red Fixative System (Cook OB-GYN) or a vial containing Cytolyte solution (Cytyc Corp., Boxborough, MA, USA). In the laboratory, an aliquot of the vortexed specimen was used to prepare a LBC preparation for cytological assessment using the AutoCyte Prep device (TriPath, Burlington, NC, USA) or ThinPrep T2000 device (Cytyc Corp.). Slides were stained by the Papanicolau method (ThinPrep) or the modification of this stain provided in the automated staining schedule of the AutoCyte equipment. The remaining cellular material (if any) was used to prepare a cell block, by centrifugation and subsequent paraffin embedding, sectioning and haematoxylin and eosin staining. The study pathologist (a subspecialist gynaecological histopathologist and cytopathologist) was blinded to the biopsy randomisation order and to the result of the Pipelle endometrial biopsy. Pathology reports on the Tao Brush specimen were issued after assessment of both the cytological slide and the cell block specimen together.

Adequacy of endometrial samples

Routine criteria for adequacy of Pipelle biopsies were applied by the Consultant Pathologists in the routine Biopsy Service. Criteria for adequacy of Tao Brush specimens depended on an assessment of both the cytological slide and the section of the cell block specimen. Adequacy of both preparations was assessed as satisfactory when sufficient cellular material was present to make a pathological diagnosis or to exclude a pathological process with confidence. Specimens described as 'barely adequate' contained scanty endometrial material that was adequate for assessment but suboptimal for exclusion of pathology. A specimen was assessed as inadequate if there was insufficient cellular material in both the cytological slide and the cell block to exclude a pathological diagnosis.

Information collected

Information was collected using a variety of procedure report forms and patient questionnaires specifically designed for the study. These were a Health Questionnaire; NEO Five Factor Inventory; General Health Questionnaire; reports on biopsy procedure(s), hysteroscopy and ultrasound; review of clinic attendance; 10-month and 24-month follow-up reports. Full details of the questionnaires are available elsewhere.[12] The gynaecologist recorded basic details of the patient's characteristics and whether or not the biopsy was successfully completed, reasons for failure and any adverse events that occurred during the investigation. The pathologist recorded the quality of the biopsy sample ('inadequate', 'barely adequate' or 'adequate') and provided a diagnosis if the sample was sufficient.

Statistical methods

'Success' of the biopsy method was defined at two stages of the biopsy process: whether or not the biopsy was physically *completed*; and whether or not the resulting sample was *adequate* for pathological analysis.

Adequacy rates were calculated firstly in relation to the number of women assigned that biopsy (the denominator being all women in the group, as per best practice 'intention-to-treat' [ITT] approach to analysis in clinical trials), but also in relation to the number of such biopsies *completed*. In the former approach, all biopsies that could not be completed, and hence collected no sample, were counted as having failed to produce an adequate sample. The statistical comparison between samplers is undertaken for the ITT data. When examining the factors that predict failed insertion, the analysis includes only patients where the biopsy was attempted, and when predicting factors associated with adequate samples, the analysis includes only biopsies that were successfully completed.

McNemar's chi-square test (with the continuity correction) was used to compare the proportion of successful biopsies between the two types of biopsy. Paired differences in percentages are presented with 95% confidence intervals (CI).

Funding and ethical approval

The trial was funded by the NHS Research and Development Health Technology Assessment Programme (number 97/17/06) and National Research Register (NRR) project number N04800845. The full study report appears in the NHS HTA Monograph series.[12] Ethical approval was obtained from the Lothian Research Ethics Committee (Ref 1702/97/6/34).

Results

Patient groups

A total of 1220 high-risk and moderate risk women were assessed for eligibility for the study, prior to their clinic appointment, but 453 were not recruited for various reasons including insufficient time for the study nurses to interview women, specific medical reasons for not participating and some investigations already completed. The remaining 767 women were eligible for the study and for 526 of these, both clinician and patient consented to her randomisation into the study. Patient characteristics are presented in Table 1. It can be seen that PMB was the predominant presenting complaint in the high-risk group, heavy vaginal bleeding and irregular bleeding in the moderate risk group.

Table 1. Characteristics of patients, by risk group

	High risk (postmenopausal)	Moderate risk (premenopausal)
Number randomised	200	326
Mean age in years (SE)	57.6 (0.57)	45.2 (0.26)
Nulliparous (%)	13	15
Currently using HRT (%)	30	9
Presenting complaint* (%)		
Postmenopausal bleeding	95	1
Postcoital bleeding	2	8
Intermenstrual bleeding	2	22
Irregular periods	5	47
Heavy periods	1	68
Other	2	8

*More than one presenting complaint could be noted by clinician, so percentages total more than 100% (107% for high-risk group and 154% for moderate risk group).

Completion of the endometrial sampling procedure

Both the Pipelle and Tao Brush sampling procedures were successfully completed in 164 of 200 postmenopausal (high-risk) women (87%), and in 275 of 326 premenopausal (moderate risk) women (84%). Neither procedure was completed in 36 high-risk women (16%) and in 43 moderate risk women (13%). In addition, for eight moderate risk women only one or other biopsy was completed (2%, five Pipelle and three Tao). Overall Pipelle was completed in 444 women (84.4%), and Tao Brush in 442 (84.0%) – very similar rates.

Failure was almost always due to an inability to insert the device into the uterine cavity – 31 high-risk women (15%) and 41 moderate risk women (13%). In the remaining women, noncompletion arose because there were medical or technical reasons for not attempting the biopsy (e.g. patient state or equipment failure). For both devices, the only factor significantly associated with failed insertion was nulliparity. Insertion of Pipelle was unsuccessful in 22% of attempts among nulliparous women compared with 8% of parous women ($P = 0.001$). Tao Brush was unsuccessful in 20% of nulliparous women and 8% of parous women ($P = 0.005$). Age, menopausal status and current HRT use were not associated with success of insertion of Pipelle or Tao Brush devices.

Adequacy of endometrial samples

In postmenopausal (high-risk) women, the Tao Brush significantly outperformed Pipelle in obtaining an adequate specimen for pathological assessment. Results are shown in Table 2. Within groups, the rates of adequate samples varied according to setting, being higher when biopsy was undertaken at the time of hysteroscopy, compared with blind outpatient biopsy. In postmenopausal women, this was statistically significant for Tao Brush (83 versus 61%, $P < 0.001$), and borderline significant with Pipelle (50 versus 36%, $P = 0.063$), but in premenopausal women (moderate risk group) the observed differences were not statistically significant.

Table 2. Percentage of adequate samples for Tao Brush and Pipelle, by setting for biopsy and overall: separately for postmenopausal and premenopausal women (for all biopsies assigned – ITT)

Group	% 'adequate' samples					
	n	Pipelle	Tao Brush	Difference in %: Tao - Pipelle	95% CI	*P* value
Postmenopausal (high risk)						
Hysteroscopy with biopsy	100	50.0	83.0	33.0	21.4–44.9	<0.001
Blind biopsy	100	36.0	61.0	25.0	14.1–35.9	<0.001
Whole group	200	44.0	72.0	28.0	20.9–37.1	<0.001
Premenopausal (moderate risk)						
Hysteroscopy with biopsy	166	81.9	77.7	−4.2	−9.9 to 1.4	0.211
Blind biopsy	160	75.6	71.3	−4.4	−10.2 to 1.5	0.211
Whole group	326	78.8	74.5	−4.3	−8.4 to −0.2	0.055

Since the analyses shown in Table 2 are intention-to-treat, some of the apparent deficit in adequate samples might be due to noncompletion of the biopsy, for medical or technical reasons, or due to failed insertion. Table 3, therefore, shows the rates of adequate samples for those women where both biopsies were completed, a characteristic of clinical importance. The rate of adequate samples when Tao Brush is used is similar in both risk groups (here around 87%), whereas with Pipelle the rate of adequate samples is much lower in postmenopausal women (52%), but slightly higher in the premenopausal women (92%). In postmenopausal women for whom both biopsies are possible, the advantage of Tao Brush over Pipelle, in terms of rate of adequate samples, is 35 percentage points (pp; $P < 0.001$, 95% CI 24–42 pp). Table 3 also reports the results by order of biopsy assigned, and bearing in mind the relatively small subgroup sizes, there is no apparent effect of order.

Analyses were undertaken to explore factors potentially associated with adequacy of tissue samples (menopausal status, age, parity or HRT use). Menopausal status was associated

Table 3. Percentage of adequate samples for Tao brush and Pipelle, by setting for biopsy and order samples taken: separately for postmenopausal and premenopausal women (for all women who had both biopsies completed)

Group	Percentage of adequate samples					
	n	Pipelle	Tao brush	Difference in %: Tao - Pipelle	95% CI	*P* value
Postmenopausal (high risk)						
Hysteroscopy with biopsy						
Brush first	42	61.9	97.6	35.7	17.6–53.8	
Pipelle first	47	51.1	89.4	38.3	18.7–57.9	
Ignoring order	89	56.2	93.3	37.1	23.7–50.5	<0.001
Blind biopsy						
Brush first	39	35.9	82.1	46.2	24.8–67.5	
Pipelle first	36	61.1	80.6	19.4	−0.2 to 39.9	
Ignoring order	75	48.0	81.3	33.3	18.8–47.9	<0.001
Whole group	164	52.4	87.8	35.4	25.5–45.2	<0.001
Premenopausal (moderate risk)						
Hysteroscopy with biopsy						
Brush first	76	96.1	92.1	−3.9	−10.8 to 2.9	
Pipelle first	69	88.4	85.5	−2.9	−13.5 to 7.7	
Ignoring order	145	92.4	89.0	−3.4	−9.6 to 2.7	0.383
Blind biopsy						
Brush first	67	94.0	85.1	−9.0	−17.2 to −0.7	
Pipelle first	63	88.9	85.7	−3.2	−13.0 to 6.7	
Ignoring order	130	91.5	85.4	−6.2	−12.6 to 0.2	0.099
Whole group	275	92.0	87.3	−4.7	−9.2 to −0.3	0.055

with adequate samples with Pipelle (92% adequate if premenopausal and 52% if postmenopausal, $P < 0.001$, chi-square test) but not with Tao Brush biopsies (87.4% adequate if premenopausal and 87.8% if postmenopausal, $P = 0.99$). In postmenopausal women, both samplers had lower rates of adequate samples in women aged over 54 years. This was more marked for Pipelle (42% adequate for those over 54 years compared with 65% for the younger women, $P = 0.01$) than for Tao Brush (82 and and 95%, respectively, $P = 0.03$). Also, in postmenopausal women, for Pipelle there was a nonsignificant increase in adequate samples among women using HRT. In premenopausal women, both samplers had lower rates of adequate samples in nulliparous women (for Pipelle 75% compared with 95%; for Tao Brush 68% compared with 90%; $P < 0.001$ for both samplers). For Pipelle, there was a nonsignificant decrease in adequate samples among premenopausal women aged over 50 years.

Endometrial hyperplasia and carcinoma

The study was not powered (nor was it designed) to detect differences between Pipelle and Tao Brush in the sensitivity and specificity for detection of malignancy. However, eight cancers (1.2%) were reported in women recruited to the study – five (3.3%) in 'high-risk' (postmenopausal) women and three (0.9%) in 'moderate risk' (pre- and perimenopausal) women. Atypical endometrial hyperplasia was identified in one 'high-risk' woman (0.6%) and two (0.7%) 'moderate risk' women. Simple hyperplasia was identified in one (0.6%) 'high-risk' woman.

Of the eight cancers, five were identified by both Pipelle and Tao Brush, and in all of these, adenocarcinoma was confirmed on subsequent hysterectomy. In one further case, Pipelle biopsy identified adenocarcinoma that was not identified in the Tao Brush specimen, but was confirmed in the subsequent hysterectomy. Two reports of malignancy were made on the Tao Brush specimen alone. As Tao Brush sampling was an unproven technique, further investigations were performed in both cases before definitive treatment was undertaken. In one such case, an endometrial polyp was identified, with reactive atypical surface epithelial changes, but no evidence of malignancy. In the other case, no abnormality was found on hysteroscopy and dilatation and curettage (D&C), but the cytological appearances were sufficiently concerning that an outside expert opinion was sought. This concurred with the diagnosis of malignancy and hysterectomy was performed. However, no malignancy was identified in the hysterectomy specimen, although the endometrium suffered from autolytic changes, which limited assessment of early or noninvasive malignant change. Of the three atypical hyperplasia cases reported, the Tao Brush detected three and the Pipelle detected two. Two of the three cases of atypical hyperplasia were confirmed by Pipelle and subsequent hysterectomy; in one case, atypical hyperplasia was not confirmed on Pipelle, and subsequent follow up has been negative.

Adverse events

The data collection forms did not seek to attribute the adverse event to the Pipelle sampler or the Tao Brush. Since an adverse event might be expected to occur more often with the first insertion, we examined whether adverse events occurred more often for one ordering than the other. However, they were found to be equally distributed among those who had Pipelle or Tao Brush endometrial sampling procedure first (for blind biopsy 14 where Pipelle was first, and 12 where Tao Brush was first, and for biopsy with hysteroscopy, 18 and 15, respectively, for Pipelle and Tao Brush first). There is thus no suggestion that one or other device was more problematic.

Patient acceptability

Although all women were asked their preference (first or second biopsy), only 270 (62%) answered the question of 439 women who had both biopsies successfully completed. It is possible that some of the nonresponse is because women either did not realise that two biopsies had been undertaken or did not have a real preference. A greater proportion of both groups of women preferred the Tao Brush biopsy to Pipelle. When asked which device was less unpleasant, 89 (33%) women preferred Tao Brush biopsy compared with 51 (19%) who preferred Pipelle ($P < 0.001$, McNemar's test).

Discussion

Pipelle endometrial biopsy is widely used as an inexpensive outpatient procedure to obtain endometrial tissue for histological assessment. Despite sampling only a small proportion of the endometrial surface[4] and having limitations in identifying focal lesions, it has been shown to have a high degree of sensitivity and specificity for the detection of endometrial carcinoma.[19] It is also useful in obtaining tissue for assessment of the phase of the menstrual cycle in premenopausal women.[20] However, the Pipelle endometrial sampler does have disadvantages. Although mostly well tolerated, in some women, the biopsy procedure causes considerable discomfort. There is a range of potential reasons for failure of use of Pipelle sampler, but most common is a scanty or absent specimen due to endometrial atrophy. There is no widely accepted definition of what constitutes an unsatisfactory endometrial biopsy, and a recent report has highlighted the need for defined pathological criteria.[6,21] Systematic reviews comparing outpatient endometrial sampling procedures[19,22] have reported that outpatient endometrial sampling has a high overall accuracy in diagnosis of endometrial malignancy in adequate samples, but it is recognised that assessment of PMB is often problematic as there may be failure to

collect an adequate sample in up to 10% of women.[5] Our study has shown that in the investigation of PMB, Tao Brush biopsy is significantly more likely to provide an adequate specimen for pathological assessment than use of the Pipelle sampler (72 versus 44%, $P < 0.001$). Among postmenopausal women for whom biopsy could be completed, the inadequate sample rate (48%) was comparable with that reported in the literature, whereas Tao Brush showed a significantly superior performance in this group (12% inadequate). In contrast, in pre- and perimenopausal (moderate risk) women with completed biopsies, a Pipelle sample was inadequate in only 8% of women compared with 13% inadequate samples with a Tao Brush. The results are similar to those of an earlier study[23] in which the Tao Brush was reported to be a reliable uterine sampling device that performed well in outpatient assessment of the endometrium of women with patent cervices.

With regard to patient factors associated with overall success of sampling (completing the biopsy and obtaining an adequate sample), premenopausal status (or in this study, risk group) is very strongly associated for Pipelle biopsies (79 versus 44% of postmenopausal, $P < 0.001$) but not for Tao biopsies (75 versus 72%). Our analyses have also shown the significance of nulliparity both at the stage of inserting the device and also in terms of the adequacy of the sample taken. Nulliparity was significantly associated with insertion failure for both Pipelle and Tao Brush (while there was no significant association with age, menopausal status or HRT use). Failure of insertion was equally common with Pipelle and Tao Brush (each 14%) comparable with small studies in the literature of failure rates varying between 3 and 14%. Once the device had been successfully inserted into the uterine cavity, the effect of parity was again significant for both Pipelle and Tao biopsies but within the premenopausal group only. For Pipelle biopsy, the inadequate rate in nulliparous women was 25% compared with 5% of parous women ($P < 0.001$). Tao Brush sampling showed a similar significant difference between nulliparous women (32.2% inadequate) and parous women (9.9%) ($P < 0.001$). This effect of parity on adequacy is independent of device insertion failure, but the explanation is uncertain. Another factor associated with inadequate samples for both Pipelle and Tao samplers was age in the postmenopausal group, in that women over 54 years had more inadequate samples.

One of the advantages of using the Tao Brush is that the technique may be more acceptable to the women than the aspiration sampling technique, especially if the uterine cavity is atrophic. Additionally, the Tao Brush samples a larger percentage of the surface area of the endometrium, and there is a relatively high (80%) level of agreement between diagnosis from the Tao Brush sample and histological diagnosis based on hysterectomy sample.[24] This technique of tissue collection does not appear to interfere with subsequent histological studies of endometrium sampled by conventional curettage or aspiration (Pipelle).

An interesting observation in this study was that in both risk groups, there was a better chance of a sample being adequate when the biopsy was taken at the time of outpatient hysteroscopy compared with 'blind' biopsy. This was statistically significant in postmenopausal women with the Tao Brush (83 versus 61%, $P < 0.001$), but a similar trend was also observed in the premenopausal group with both devices. The difference was also significant for both Pipelle ($P < 0.04$) and Tao Brush ($P < 0.009$) when data for both risk groups were combined. It is possible that gas insufflation of uterus for hysteroscopy may have in some way helped in the subsequent taking of endometrial samples. A possible confounding factor is the experience of the operator collecting the sample. This was a pragmatic trial in which it would not have been feasible to randomise the operator, and it may be that clinicians undertaking hysteroscopy were more experienced at endometrial sampling.

Previous studies have noted the effect of HRT on adequacy of endometrial biopsies, where it was reported that continuous combined HRT usage improved the proportion of 'unassessable' samples from 63% in nonusers to 41% in users. Sequential HRT further increased sample adequacy, with only 18% of samples being unassessable. In our study, the type of HRT regimen was not specifically recorded, but overall, HRT users in the high-risk postmenopausal group also had an improved inadequate rate with Pipelle (38% in users and 51% in nonusers). However, this did not reach statistical significance ($P = 0.16$). With Tao Brush, inadequate sample rates were already low in the postmenopausal group, but there was a slight improvement in adequacy if HRT was used, from 17% inadequate in nonusers to 10% in users.

This study was not designed nor did it have power to detect differences between Pipelle and Tao Brush samplers in sensitivity, specificity and positive and negative predictive values for diagnosis of endometrial malignancy. There was one definite and one possible false-positive malignancy with Tao Brush biopsy. Del Priore *et al.*[15] compared Pipelle and Tao Brush biopsies in 101 women in whom there was a high level of clinical suspicion for endometrial cancer. Results of Pipelle and Tao Brush biopsies were correlated with final diagnosis from hysterectomy or D&C. There were 22 cases of cancers or atypical hyperplasia, and both devices showed 100% specificity and positive predictive value with negative predictive value of 98%. Sensitivity of Pipelle was 86% and Tao Brush was 95.5%, and when both devices were used together, the positive and negative predictive values for detecting or excluding endometrial cancer were 100%.

The design of the study, with paired comparison of the two sampling devices, did not allow a straightforward comparison of their cost-effectiveness since if one device failed to provide an adequate sample the other device frequently did so, and

there was no need for the clinician to take any further action (and incur costs). At the time of the study, the marginal additional cost of Tao Brush biopsy to Pipelle biopsy was approximately £100.

Conclusion

This study has demonstrated that in postmenopausal women, Tao Brush sampling is superior to Pipelle endometrial biopsy in obtaining an adequate sample, while in premenopausal women the Pipelle sampler may perform marginally better. There is, therefore, a case for recommending the Tao Brush as a replacement for the Pipelle sampler in the postmenopausal group. It is suitable for outpatient use, and is preferred by patients to the Pipelle sampler. However, it remains an invasive procedure, it incurs slightly greater costs and pathologists require training in the interpretation of these specimens. Consequently, it is not currently available in most laboratories. As our study found little difference in adequacy of Tao Brush specimens obtained after Pipelle biopsy compared with those taken before Pipelle (86% adequate versus 90%), the place of Tao Brush biopsy might therefore be as an adjunct to a Pipelle endometrial biopsy in postmenopausal women, particularly for older women or when the operator is aware that the Pipelle sampler has yielded a scanty specimen.

Contribution to authorship

A.R.W.W.: pathology assessments, design of study, data analysis and preparation of manuscript. S.B.: clinical assessments and preparation of manuscript. A.J.L.P.: data analysis, preparation of manuscript. P.W.: data analysis and review of manuscript. H.O.D.C.: concept and design of study, clinical assessments and review of manuscript.

Details of ethics approval

Ethical approval was obtained from the Lothian Research Ethics Committee (Ref 1702/97/6/34).

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