

# Endometrial sampling and general practice

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## SUMMARY

*Endometrial sampling is an 'office' technique that has gained widespread acceptance in the United States (US). It is as accurate as dilatation and curettage (D&C) in the diagnosis of endometrial atypia and carcinoma. It appears to be the most suitable method of endometrial assessment for general practice. It has the potential for the earlier detection of endometrial abnormality and for increasing the number of women with abnormal vaginal bleeding who can be wholly managed within primary care. However, research is lacking on the effect of the widespread introduction of the technique into general practice. This paper puts forward recommendations for the use of endometrial sampling by general practitioners (GPs) based on current evidence.*

**Keywords:** endometrial neoplasm; diagnostic techniques; menorrhagia; post menopausal women.

## Introduction

THE concept of 'office' endometrial sampling has gained wide acceptance in the US. Within the United Kingdom (UK) the introduction of the technique into hospital practice has been slower but 'office' sampling is now becoming more common. At present it is rare for GPs to undertake endometrial sampling. In the US it is described as an 'office technique' as there is no need for general anaesthesia or elaborate equipment. What is the evidence that the technique is accurate and that it should become a routine tool in British general practice?

### *The technique of endometrial sampling*

Until recently, the standard method of endometrial assessment was by D&C. The procedure requires general anaesthesia and has complications such as uterine perforation,<sup>1</sup> haemorrhage and infection.<sup>2</sup> It is also known that this method obtains tissue from less than 50% of the uterine cavity in 60% of procedures,<sup>3</sup> and is not a form of treatment.<sup>4</sup>

Grimes compared D&C with a form of endometrial sampling using the Vabra aspirator (VA) and concluded in 1982 that 'D&C probably should not be the primary procedure used for obtaining most samples of endometrium.'<sup>5</sup> Endometrial sampling with the VA requires no anaesthetic and has few complications. The difficulty with the VA and similar devices, such as the Novak curette, is that they cause discomfort to some women and require a motorized pump with capital outlay. Newer sampling devices, such as the Pipelle<sup>6,7,8</sup> and the Z-sampler,<sup>9</sup> use an integral plastic piston to generate negative pressure to aspirate tissue. This avoids the need for a motorized pump and is more comfortable for the patient. The most extensively studied 'office' sam-

pler is the Pipelle. It has been studied in comparison with the VA,<sup>10,11</sup> Novak curette,<sup>12,13,14,15,16</sup> Tis-u-trap,<sup>17</sup> Accurette and Explora.<sup>18</sup> The Pipelle is equal to or better than these samplers with regard to histological analysis and patient comfort. Although it samples only 4.2% of the endometrial surface area compared with 41.6% by the VA,<sup>10</sup> it produces a greater quantity of total tissue.<sup>11</sup> The Z-sampler has been studied in comparison with the Novak curette<sup>19,20</sup> and the Gynocheck.<sup>21</sup>

Studies comparing the Pipelle<sup>22,23,24,25</sup> and the Z-sampler<sup>26</sup> with D&C, where sampling was performed on patients of various ages prior to D&C, are presented in Table 1. The studies report agreement in histological findings in 61.8–90.3% of cases (80.7% overall). Most differences were not significant. It is clear, however, that none of these techniques detect all cases of atypia or carcinoma. There appears to be no greater accuracy of one method of biopsy over the other. The recommendation of one of the groups of authors<sup>23</sup> was that caution should be used with the Pipelle if the sample is insufficient or atypical cells are present. Studies using Pipelle sampling in patients of various ages with known endometrial carcinoma prior to hysterectomy<sup>27,28,29</sup> are presented in Table 2.

The initial study by Stovall *et al*<sup>27</sup> showed the Pipelle sampler detecting 39 cases of carcinoma and one case of atypia in 40 patients with known endometrial carcinoma. This represents a sensitivity of 97.5% for adenocarcinoma and 100% for significant abnormality if it is accepted that atypia demands a more definitive assessment of the uterine cavity. Subsequent studies showed a lower sensitivity of 67.6%<sup>28</sup> and 92.3%<sup>29</sup> respectively for adenocarcinoma, although in the study with the lower figure 16.2% were diagnosed as having atypia.<sup>28</sup> These later studies differed from Stovall *et al*<sup>27</sup> in that all the patients had undergone D&C prior to Pipelle sampling. In addition, there was a variation in the rates of inadequate histological sampling (adequate defined as providing enough endometrial tissue to allow determination of endometrial morphology histologically) with none reported by Stovall *et al*<sup>27</sup> and Zorlu *et al*,<sup>29</sup> and 16.2% by Ferry *et al*.<sup>28</sup>

One study compared the Z-sampler and Novak curette in the diagnosis of endometrial carcinoma with sampling performed prior to hysterectomy.<sup>20</sup> Of 80 women with endometrial carcinoma, 44% were diagnosed by 'office' samplers, 26% by D&C, and 30% retrospectively. The Z-sampler had a diagnostic accuracy of 82.5%, with 3.8% of cases being diagnosed as atypical hyperplasia. There was a 12.5% rate of inadequate specimens. There was no statistically significant difference in the diagnostic accuracy of the two devices.

Endometrial sampling has a definite small false negative rate. In a study of 263 patients with post or peri-menopausal bleeding problems who were followed up for a minimum of 23 months, 2% went on to develop a uterine malignancy despite a negative initial endometrial biopsy ('office' or D&C).<sup>30</sup> The study was non-interventional and the decision to re-biopsy or perform hysterectomy was at the discretion of the physician. A third of the original cohort underwent further evaluation. The authors state that they 'feel it is prudent to further evaluate patients ... with a negative initial biopsy if they continue to have persistent bleeding.'

Some of the studies using the Pipelle and Z-sampler have reported endometrial carcinoma not found at hysterectomy.<sup>20,27</sup> It is possible that the lesions were fully curetted by the devices.

In 3–10% of patients, endometrial tissue cannot be obtained

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**Table 1.** Studies of endometrial histology where endometrial sampling is performed prior to D&C.

First author Year of publication	Sampling device	Study group Country of study	Number of subjects undergoing both procedures	Concordance	Total number of subjects with atypia	Total number of subjects with carcinoma	Differences in cases of atypia and carcinoma
Fothergill 1992 <sup>22</sup>	Pipelle	Immediately pre-D&C UK	187	164	Not given	4	3 atypia detected by Pipelle sampling but not by D&C
Law 1993 <sup>23</sup>	Pipelle	Immediately pre-D&C UK	191	118	8(+2 atypia Pipelle but carcinoma D&C)	8(incl. 2 with carcinoma D&C but atypia Pipelle)	2 atypia on Pipelle sampling were carcinoma on D&C. In addition, 3 atypia with D&C were not detected by Pipelle
Goldchmit 1993 <sup>24</sup>	Pipelle	Immediately pre-D&C Israel	176	159	0	3	There were 2 cases of complex hyperplasia. In 1 of these, Pipelle gave endometritis
Batool 1994 <sup>25</sup>	Pipelle	In outpatients within 4 weeks of D&C UK	55	48	0	3	No significant differences
Phua 1992 <sup>26</sup>	Z-sampler	In outpatients within 47 days of D&C Singapore	48	41	0	3	No significant differences

with the Pipelle because of patient discomfort, vaginal adhesions, narrow cervical os, or retroverted uterus.<sup>9,31</sup> The Pipelle samplers do seem to be suitable for use in general practice, as the procedure can be performed by any doctor who has experience in inserting a uterine sound;<sup>32</sup> within a single family health services authority, 75.4% of practices submit claims for the fitting of intrauterine contraceptive devices (personal communication: Staffordshire FHSA, 1995). However, so far, studies in general practice are only on small sample sizes and of a descriptive nature.<sup>33,34</sup>

Thus, endometrial sampling using flexible integral piston devices appears suitable for general practice, although studies within general practice are lacking. The devices are as accurate as D&C but they do have a small false negative rate. Are alternatives to endometrial sampling more accurate and appropriate?

### Transvaginal ultrasonography

The thickness of the endometrium can be determined by transvaginal ultrasonography.<sup>35</sup> Studies indicate a good negative predictive value in patients with endometrium of  $\leq 5$  mm double thickness (i.e. both layers of endometrium).<sup>24,36,37,38</sup> Some authors recommend lower values,<sup>39</sup> and a case of endometrial carcinoma has been described in a woman with an endometrial thickness of 3.2 mm.<sup>40</sup> There is no specific ultrasonic appearance of endometrial malignancy, and even in combination with colour doppler imaging of blood flow it does not reliably distinguish benign from malignant lesions.<sup>41</sup> If the endometrial thickness is high, diagnostic endometrial assessment is recommended. Transvaginal ultrasonography appears to be acceptable to women<sup>35</sup> and has few complications.

In a study using transvaginal ultrasonography and Pipelle endometrial sampling prior to hysteroscopy and curettage or hysterectomy, all six cases of endometrial carcinoma were detected by the Pipelle, and all women with endometrial carcinoma had an endometrial thickness exceeding 12 mm. The study group involved 126 women with post-menopausal bleeding who underwent both sampling and sonography successfully.<sup>39</sup> The authors propose the combined use of both transvaginal ultrasonography and endometrial sampling as an office-based approach to post-menopausal endometrial disease.

If transvaginal ultrasonography has a role in determining which patients should undergo further endometrial assessment, it is not suitable for widespread use within general practice premises. Transvaginal ultrasonography has a significant capital outlay and running cost, and a high degree of skill is required in undertaking the procedure. Not many GPs possess any experience in performing ultrasonography. As 'office' endometrial sampling is simpler to use in general practice, the place of secondary care ultrasonography may be for women in whom sampling has failed, in order to select those for hospital-based endometrial assessment.

### Hysteroscopy

Hysteroscopy is the most accurate method of assessing the endometrium.<sup>42,43</sup> It can be performed in the outpatients department but, in the UK, many hospitals lack this facility, necessitating inpatient assessment under general anaesthesia.<sup>44,9</sup> The rigid device used for outpatients is 4 mm in diameter, which is comparable to the 3.1 mm external diameter of the flexible Pipelle sampler. However, if biopsy is required during hysteroscopy, insertion of the biopsy forceps requires a wider diameter instrument.<sup>44</sup>

The outpatient procedure appears to be acceptable to women<sup>45</sup> with few complications.<sup>44</sup> In a study comparing the Pipelle with outpatient hysteroscopy and ultrasound in post-menopausal bleeding, 24 out of 119 patients were considered inappropriate for outpatient assessment, although no reason was given.

**Table 2.** Pipelle endometrial sampling in patients with known endometrial carcinoma.

First author Year of publication	Study group - place of sampling and method of diagnosis of endometrial carcinoma. Country	Number of subjects	Number Pipelle diagnosed as carcinoma	Number Pipelle diagnosed as atypia	Number Pipelle diagnosed as insignificant
Stovall 1991 <sup>27</sup>	'Office' within 4 weeks of hysterectomy: 30% diagnosed by D&C; 70% by various samplers USA	40	39	1	0
Ferry 1993 <sup>28</sup>	Under general anaesthesia prior to hysterectomy: diagnosis by D&C Australia	37	25	6	6
Zorlu 1994 <sup>29</sup>	Outpatients prior to hysterectomy: diagnosis by D&C Turkey	26	24	0	2

Sampling failed in 10% and missed two cases of atypical hyperplasia. One of these cases was also missed on hysteroscopy and only diagnosed at hysterectomy following abnormal glandular cytology on cervical smears. One case of adenocarcinoma was diagnosed by the Pipelle as atypia, and initial hysteroscopy failed owing to mucus and pus and was only successful after local oestrogen therapy; however, it showed visual abnormality, with the biopsy indicating hyperplasia, although the hysterectomy specimen showed adenocarcinoma.<sup>46</sup>

When the Z-sampler is used prior to hysteroscopy,<sup>9</sup> the sampling device is shown to be accurate in detecting serious pathology. In 70 patients sampled, the sampler detected the four cases of adenocarcinoma detected by hysteroscopy. In 36 patients, insufficient material was obtained by the sampler, and hysteroscopy showed 30 normal or atrophic uteri and six benign polyps. The authors state that if no tissue is obtained at endometrial biopsy, this is a good prognostic finding in post-menopausal women. They recommend office sampling with hysteroscopy for women with post-menopausal bleeding if further bleeding occurs.<sup>9</sup> Other authors agree with office sampling for post-menopausal bleeding.<sup>25</sup>

Like transvaginal ultrasonography, hysteroscopy has a significant capital outlay and running cost, and a high degree of skill is required in undertaking the procedure. It is not suitable for widespread use within general practice premises.

A 'one-stop' menstrual problem clinic using outpatient hysteroscopy and transvaginal ultrasonography within secondary care has been described.<sup>47</sup>

### *The need for endometrial assessment*

Carcinoma of the endometrium accounts for about 2000 deaths per year in England and Wales. It is rare under the age of 35 years but the incidence begins to rise exponentially to peak in the post-menopausal age group. Around the age of 48 years it becomes more common than carcinoma of the cervix.<sup>48</sup> However, the five-year mortality rates for the disease are better than for cervical cancer. The earlier the diagnosis of cancer of the body of the uterus is made, the better the survival rate. This is true with regard to both age and stage of disease.<sup>49</sup> The presentation of the disease is usually by abnormal vaginal bleeding. The diagnosis is made by histological examination of the endometrium.

In the post-menopausal woman, it is generally accepted that endometrial assessment is necessary in order to exclude carcinoma of the endometrium. However, fewer than 10% of women with post-menopausal bleeding will have endometrial cancer.<sup>9,50-52</sup> In women under the age of 35 years, the condition is extremely rare.<sup>48</sup>

The peri-menopausal woman presents a more difficult dilemma for a GP. Routine practice in the US is that any woman with abnormal vaginal bleeding over the age of 40 years requires

endometrial assessment,<sup>53,54</sup> and hospital management in the UK tends to follow these lines. The behaviour of GPs in the UK suggests that they do not necessarily accept this view.<sup>55</sup> It is known that 15% of the population over the age of 40 years have menorrhagia;<sup>56</sup> irregular periods in this group are common<sup>57</sup> and 30% of women aged 35 years and over regard their periods as fairly heavy or very heavy.<sup>58</sup> These studies give a point prevalence for these symptoms, and thus the percentage of women experiencing these symptoms at any time between the age of 40 years and the menopause is much higher.

It is not known what specifically influences GPs when deciding who they would refer to secondary care. There may be an under-investigation of women, or GPs may be able to identify women at a higher risk of serious endometrial pathology. There are well-described risk factors for endometrial carcinoma.<sup>54</sup> The factors influencing GP referral behaviour in the management of abnormal vaginal bleeding have not been studied. The reasons for any delay in diagnosis of endometrial carcinoma are not known.

The use of endometrial sampling by GPs as an initial screening test for hospital referral appears attractive. However, as with any screening test, there is the potential for missed lesions and harm from over-treatment.

### *The natural history of endometrial carcinoma*

Histological examination of the endometrium recognizes three major groups of neoplastic change: endometrial hyperplasia; atypical endometrial hyperplasia characterized by cellular atypia; and endometrial carcinoma. The term 'complex hyperplasia' refers to hyperplasia with architectural or cellular atypia. Twenty-three per cent of cases of atypical hyperplasia progress to adenocarcinoma, as do 1.2% of cases of endometrial hyperplasia.<sup>59</sup> It is not known whether all cases of endometrial carcinoma develop from atypical hyperplasia or whether some arise *de novo*. Not all cases of adenocarcinoma have evidence of hyperplasia.<sup>60</sup>

The incidence of reported endometrial carcinoma is significantly higher in the US than in England and Wales,<sup>61</sup> although death rates are similar.<sup>62</sup> In the US, screening a population of asymptomatic women produces an incidence of endometrial carcinoma higher than expected considering the incidence of overt carcinoma. This raises questions concerning the natural history of endometrial carcinoma and whether or not these occult carcinomas are biologically significant.<sup>63</sup> It may be that they remain occult for the remainder of a patient's life, or indeed regress. The more widespread use of endometrial sampling by GPs may lead to an over-treatment of some women.

The screening of asymptomatic women for endometrial carcinoma is not recommended in Canada because of the lack of evidence concerning the clinical effectiveness of a screening proce-



ture,<sup>64</sup> although it is recommended in the US if the woman is at high risk.<sup>65</sup>

## Recommendations

Endometrial sampling by GPs is practical and, under the current system of funding, is probably cheaper as a single procedure than that provided by secondary care. However, hard-pressed primary care staff do not usually welcome additions to their workload unless they are accompanied by additional resources.<sup>66</sup> The widespread introduction of endometrial sampling into primary care would certainly result in an increase in the number of perimenopausal women undergoing the procedure, with financial and workload implications for pathology laboratories and GPs. This might lead to the earlier detection of endometrial carcinoma and improved prognosis; however, the possibility of biologically insignificant lesions being detected counters the argument for an overall improvement in morbidity and mortality.

Computer modelling of cost-effectiveness in the management of post-menopausal bleeding — comparing observation unless bleeding recurred, office endometrial sampling, D&C and hysterectomy — concluded that office sampling is always preferable to D&C or hysterectomy for the initial evaluation.<sup>67</sup>

Current opinion recommends endometrial assessment in all cases of post-menopausal bleeding. The suitability of office sampling to general practice suggests that it should be performed by trained GPs. If bleeding re-occurs, referral to secondary care should take place for a definitive diagnosis by hysteroscopy or hysterectomy.

Research is lacking on the causes of delays in the diagnosis of endometrial carcinoma in peri-menopausal women, the effect of the elimination of the delay on mortality and morbidity, and the effect of the widespread introduction of endometrial sampling by GPs. However, on current evidence, GPs should consider the diagnosis of endometrial carcinoma in all women over the age of 40 years presenting with increased vaginal bleeding. If the GP feels that the woman is at risk, endometrial sampling should then take place by a trained doctor. If medical treatment fails, referral to secondary care should take place for definitive diagnosis by hysteroscopy or hysterectomy.

### RECOMMENDATIONS

- The initial assessment of post-menopausal bleeding should involve endometrial sampling by a trained general medical practitioner.
- If a woman has further post-menopausal bleeding or the sample shows atypia or carcinoma, referral to secondary care for hysteroscopy or hysterectomy should take place.
- GPs should consider the possibility of endometrial carcinoma in menstruating women over the age of 40 years with a menstrual disturbance of increased or irregular loss.
- If the clinician feels there is a significant risk, endometrial sampling should be performed by a trained GP.
- Referral to secondary care for hysteroscopy or hysterectomy should take place if the endometrial sample shows atypia or carcinoma, or if medical treatment has failed.

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