An assessment of the Mi-Mark endometrial sampling technique

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SUMMARY One hundred and twenty cytological smears and 106 histological specimens were obtained from 115 patients using a new technique of endometrial sampling. It proved an atraumatic procedure and was well accepted by the patients. Some problems were encountered in the preparation of satisfactory cytological specimens and in their interpretation. The method was not completely reliable for detecting endometrial pathology and is therefore considered unsuitable for monitoring patients on hormone replacement therapy. It was found to be useful as a gynaecological outpatient technique for sampling the endometrium when formal curettage was unsuccessful, in avoiding the necessity for a preoperative curettage to confirm suspected carcinoma, and in the investigation of infertility.

There is increasing evidence that the use of oestrogenic hormone replacement therapy for menopausal symptoms increases the incidence of endometrial carcinoma (Antunes *et al.*, 1979; Jick *et al.*, 1979). This has emphasised the need for a simple and effective technique for endometrial sampling so that these patients can be regularly screened for endometrial pathology (Studd *et al.*, 1979).

The Mi-Mark helix has been developed by Milan and Markley (1973) to overcome some of the disadvantages of the various brushes, aspirators, and jet washers that have been used previously to sample the endometrium. It is made of flexible plastic and can be inserted into the uterus without pain or danger of perforation. The subsequent preparation of the specimen is simple, and frequently material can be obtained for both cytological and histological examination.

Milan *et al.* (1976) and Markley and Milan (1979) have reported good cytological results using the technique as a screening method on women over the age of 40. As they followed up only their positive cases with curettage their estimate of false-negatives is inadequate. The present investigation was undertaken in order to assess the technique more fully.

Patients and methods

A total of 124 Mi-Mark specimens were obtained

from 115 gynaecological patients. The age range of the patients was 21-80 years and their presenting complaints are shown in Table 1. Fifty-three samples were taken at the outpatient clinic in order to assess the patients' reaction to the method. Twenty-three of these patients also had a formal uterine curettage performed on another occasion. Seventy-one Mi-Mark samples were taken in theatre immediately preceding curettage or other operative procedure. The purpose of this group was to check the completeness of sampling of the endometrium and to document any misdiagnoses.

Table 1 *Presenting complaints of the 115 patients*

Menstrual abnormalities	52
Postmenopausal bleeding	35
Infertility	13
Abdominal pain	2
Incontinence	1
Vulval warts	1
Unspecified	8
Abnormal cervical smear	2
Oophorectomy/Ca. breast	1

The Mi-Mark helix and the details of the technique have been described in full elsewhere (Milan and Markley, 1973; Milan *et al.*, 1976; Husemeyer and Gordon, 1979). The Mi-Mark Sterile Endometrial Sampling Kit (Simpson/Basye Inc) contains two disposable plastic instruments (Fig. 1). The helix itself has semisharp edges designed to abrade the

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Fig. 1 The Mi-Mark helix and sound/paddle.

endometrial lining and a matt surface which encourages adherence of the specimen. The other instrument has two functions: one end is a thin sound which can be used to dilate the cervix and feel the direction of the uterus; the other end is a flattened 'paddle' with a central slot through which the helix is passed in order to remove the entwined specimen. Also included in the kit is a solution for lysis of red cells and an alcoholic fixative for the cytological smears.

A cervical smear was obtained first, and in the earlier cases the uterus was routinely sounded. The sounding was not found to be particularly useful and was later abandoned. The helix was inserted into the uterus and, using a rotational 'screwing' movement, the endometrial sample entwined in mucus was collected and withdrawn. The material was deposited on the flat paddle by passing the whole length of the helix through the slot, and the paddle was then used to make cytological smears. The slides were put into the lysing solution for 15 minutes and then fixed. They were stained by the Papanicolaou method.

Any remaining material on the paddle was fixed in 10% formol saline for histological processing. In some of the later cases the whole of the first specimen was used for cytology and the helix was reinserted to obtain a second specimen for histology. The histological material was embedded in paraffin wax using routine techniques, and sections were cut at three levels through the block and stained with haematoxylin and eosin. Curettage specimens were processed similarly, although only one level was cut routinely. Hysterectomy specimens were examined macroscopically, and suitable blocks were taken for histology and processed in the same way.

Seven of the patients had two Mi-Mark examinations and one patient had three such examinations. The procedure was well accepted by all the patients and was not found to be painful.

Results

CYTOLOGY

One hundred and twenty cytological smears were

examined (Table 2). In those cases where the slide preparations were satisfactory there was excellent material for microscopy. The endometrial epithelium was present in sheets and frequently in a tubular double layer representing the endometrial glands (Fig. 2). Endometrial stromal cells were also present in varying numbers but examination of these did not produce any useful information.

Table 2 Numbers and adequacy of Mi-Mark specimens

Number of patients	115
Number of Mi-Mark specimens	124
Cytology and histology	102
Cytology only	18
Histology only	4
Inadequate cytology specimens	35 (30%)
Inadequate histology specimens	47 (45%)
Patients with no adequate Mi-Mark	15 (13%)

Cyclical changes were observed in the endometrial epithelium. In the proliferative phase the nuclei were regularly arranged, round or oval in shape, and showed minimal variation in size. They contained chromatin clumps and one or two prominent nucleoli (Fig. 3). Mitotic figures could be found with careful scrutiny but they were not a prominent characteristic. In the early secretory phase the nuclei appeared similar to those in the proliferative phase but the nuclear cytoplasmic ratio decreased so that they appeared more spread out. In well-spread specimens perinuclear vacuolation could be seen (Fig. 4). In the later secretory phase, the nuclei had a uniform finely granular chromatin pattern and usually no nucleoli. The secretory phase was identified cytologically in 13 out of 17 patients in whom the Mi-Mark histology showed secretory endometrium. In menstrual endometrium degenerate endometrial cells were closely associated with polymorphs.

Inactive endometrium from patients on oral contraceptives showed epithelial cells with more cytoplasm and less prominent chromatin clumping and nucleoli than proliferative phase cells. Benign endometrium from postmenopausal patients consisted of sheets of cells of uniform size.

Hyperplasia was diagnosed confidently in only two of 10 patients who had evidence of it in curettings. The cytological characteristics were nuclear pleomorphism, cell crowding, and coarse chromatin clumping. Similar but less pronounced changes were seen in a further four patients, all of whom were postmenopausal. Two of these patients proved to have endometrial polyps, one had cystic endometrial hyperplasia, and no curettings could be obtained at curettage in the fourth.

Adenocarcinoma was diagnosed in three patients

Fig. 2 *Tubular fragment of endometrial epithelium in a cytological preparation. Papanicolaou $\times 280$*

Fig. 3 *Proliferative endometrium in a cytological preparation. The nuclear cytoplasmic ratio is high. The nuclei vary in size and have prominent nucleoli. Papanicolaou $\times 830$*

and showed the usual cytological features of this tumour (Fig. 5).

Abnormal squamous cells were seen in cytological preparations from three patients. One had the appearances of dyskaryosis associated with cervical dysplasia and carcinoma-in-situ which was subsequently confirmed by the histology of a cone biopsy. One of the patients with adenocarcinoma also had dyskaryotic squamous cells in the smear. Curettage showed this to be an adenosquamous endometrial

carcinoma. The third patient had dyskaryotic squamous cells in the cervical smear as well as in the endometrial sample, and she is being followed up with cervical cytology. Endocervical epithelium as well as endometrial epithelium was usually present in the cytological specimens and sometimes caused diagnostic difficulties. The endocervical cells were often closely associated with the endometrial cells, and in some cases they showed inflammatory changes which were difficult to differentiate from hyperplastic

Fig. 4 *Secretory endometrium in a cytological preparation. The nuclear cytoplasmic ratio is less than in Fig. 3. The nuclear chromatin is evenly distributed, and nucleoli are less prominent. Perinuclear vacuolation is present. Papanicolaou $\times 830$*

Fig. 5 *Endometrial adenocarcinoma in a cytological preparation. Papanicolaou $\times 830$*

endometrial cells. Comparison with cells in the cervical smear was helpful.

HISTOLOGY

One hundred and six Mi-Mark specimens were available for histological examination (Table 2). The diagnostic criteria used were those well established

from the routine study of curettage specimens. Comments were made as to the physiological status of the endometrium, for example, proliferative, secretory, inactive, atrophic, or 'pill effect', and the presence of any pathological features was noted. Examples of proliferative and secretory patterns and of adenocarcinoma are shown in Figure 6.

Fig. 6 Examples of satisfactory Mi-Mark histology specimens: (a) proliferative phase endometrium; (b) secretory phase endometrium; (c) adenocarcinoma. Haematoxylin and eosin $\times 52$

ASSESSMENT OF RESULTS

Adequacy of specimens (Table 2)

Thirty per cent of the cytology smears contained too little endometrial material upon which to base an opinion. The quality of the smears was also variable, some areas being too thick for microscopy and other areas having partially lysed blood obscuring the nuclear detail of the cells. Increasing the length of time in the lysing solution did not improve this.

In 45% of the histological preparations there was insufficient tissue for diagnosis. These contained mucus with only individual cells or superficial strips of epithelium and no adequate fragments of endometrium.

In 15 patients neither cytological nor histological preparation was adequate for assessment, but in three of these no uterine curettings could be obtained either. There were two additional patients with cervical stenosis in whom the helix would not enter the endometrial cavity at all. In contrast, there were 10 patients in whom formal curettage produced no tissue but from whom a Mi-Mark sample was considered adequate for at least one examination. The average age of the patients whose specimens were adequate for both cytology and histology was 40 years whereas those with only one or with neither specimen adequate were average 49 and 48 years respectively. This suggests that adequate samples

were more often obtained from premenopausal patients.

Confirmation of Mi-Mark findings (Tables 3 and 4)
The comparison of the Mi-Mark (combined cytology and histology) results and the histology of the uterine curettings is shown in Table 3. In those cases where the Mi-Mark specimen was considered inadequate, the curettings gave more information both as to the physiological state of the endometrium and also in the detection of pathological conditions. In 28 cases (37%) where the Mi-Mark sample was considered adequate for a cytological or histological opinion (or both), the curettings still gave more information. Fourteen pathological lesions were found to have been missed by the (adequate) Mi-Marks. Although it may be considered that some of these (eg, endo-

Table 3 Comparison of Mi-Mark results with uterine curettage

	Mi-Mark	
	'Adequate' n = 100	'Inadequate' n = 15
Number who had D & C	75	13
Curettings unobtainable or inadequate	10	3
Curettings gave more information	28 (37%)	10 (77%)
(a) Physiological state	20	10
(b) Pathological conditions	14	6

Table 4 Detection of significant 'cavity' pathology by Mi-Mark

Pathology	Detected	Not detected
Endometrial carcinoma	3	1
Endometrial hyperplasia	3	7
Endometrial polyp	1	3
Endometritis	1	2
Endocervical polyp	0	8

cervical polyps) were not very significant, four hyperplasias and one carcinoma were missed.

Further information on pathological lesions was obtained from hysterectomy specimens, and a summary of the detection of pathology by the Mi-Mark is shown in Table 4.

Two of the hysterectomy specimens provided further evidence of incomplete sampling of the endometrial cavity by the Mi-Mark technique. Figure 7 shows a montage of histological sections of the full length of the endometrial cavity from a hysterectomy specimen in which the Mi-Mark examination was made in theatre immediately before hysterectomy. With the microscope the superficial abrasion of the endometrium could be clearly seen, and it extends 4 cm in from the external os. It stops

short of the large endometrial polyp which originates from the fundus and is seen in the parallel section. It is probable that because the helix is flexible it was bent over by the polyp and prevented from sampling the distal part of the cavity. As shown in Table 4, only one out of four endometrial polyps was detected by the Mi-Mark technique.

Two of the carcinomas in this series were found to be relatively localised lesions. One is shown in Fig. 8 where, after a preoperative Mi-Mark examination, the helix was reinserted and left in situ during the hysterectomy. In this case malignant cells were found on cytological examination but the Mi-Mark histology showed proliferative endometrium only. Figure 9 shows histology from the other small carcinoma. The endometrial fragments seen in the Mi-Mark specimen clearly correspond with the small 'bites' missing from the endometrium in the hysterectomy specimen. These are from areas of normal endometrium, and the tumour has not been sampled. In this case the cytological smear was inadequate and so the tumour was not detected by the Mi-Mark technique.

In the 13 premenopausal patients undergoing investigation for infertility the technique was found to be useful. Cycle staging was possible in nine of

Fig. 7 Montage of histological sections from a hysterectomy. The total length of the uterine cavity was 7.5 cm. The 3.5 cm length polyp arising from the fundus is seen in the parallel section. The superficial abrasion caused by the Mi-Mark examination extended only 4 cm from the external os. H and E.

Fig. 8 *Hysterectomy specimen with helix in situ. Arrows show an area of roughening which proved to be a small carcinoma.*

Fig. 9 *Histological sections from the case of endometrial carcinoma not detected by the Mi-Mark technique. (a) Mi-Mark histology. Proliferative endometrium. (b) Section from hysterectomy showing endometrial 'bites' removed by Mi-Mark. (c) Adjacent area of carcinoma not sampled by either histology or cytology. H and E $\times 20$*

these, seven in the secretory phase providing evidence of ovulation. In three patients the cycle could not be staged from the Mi-Mark specimen but curettage gave accurate information. One patient could not be staged on either Mi-Mark or curettings.

Discussion

The Mi-Mark technique has been developed for obtaining samples of endometrium from outpatients without an anaesthetic (Milan and Markley, 1973). The procedure was well accepted by patients and was not painful. No objection was made to inserting the helix more than once or to repeating the procedure on a second occasion. In this respect the device is superior to others where pain and discomfort are not uncommon (Hutton *et al.*, 1978; Haack-Sørensen *et al.*, 1979). The helix appears to be safer than more rigid sampling devices, and the chances of uterine perforation are negligible. Deliberate attempts to perforate a uterus removed at hysterectomy with the helix resulted only in buckling the instrument.

The specimen is simple to recover and there is the added advantage of obtaining samples for both cytology and histology in some cases. The laboratory processing uses the already well-established methods for cytology of cervical smears and histology of uterine curettings.

When the cytological smears were adequate and thinly spread they provided good material for staging the menstrual cycle and screening for malignancy. It was necessary to adapt cytological criteria from those used for exfoliated endometrial cells to the appearances of sheets of freshly obtained endometrial epithelium in the Mi-Mark specimens. The cytological appearances observed in the normal endometrial material correlated with those described in histological material by Dallenbach-Hellweg (1975) and were similar to those reported in endometrial aspirates by Reagan and Ng (1973). It was found that endometrial hyperplasia could not be diagnosed reliably from the cytological material. This confirms the experience of Studd *et al.* (1979) with the Isaacs endometrial sampling device. However, in some cases atypical features were noted and curettage would have been recommended if this were being used as a screening procedure. It is probable that further experience with the Mi-Mark technique would result in better understanding of the cytological appearances. The slide preparations of the cytological material could be improved with closer attention to detail and the avoidance of thick smears. The mixture of endometrial and endocervical epithelium could be reduced with a modification of the helix in which a tubular sleeve or guard could be used to protect the endocervix from abrasion.

The large number of inadequate specimens could probably be reduced by routinely inserting the helix twice and taking one sample for cytology and the other for histology. In postmenopausal patients with atrophic endometrium it may still prove difficult to obtain adequate specimens.

The low pick-up rate for endometrial pathology is disappointing. One missed carcinoma is not uncommon in reports of other endometrial screening techniques (Wachtel *et al.*, 1973; Isaacs and Ross, 1978; Studd *et al.*, 1979), but the low rate of detection of other endometrial lesions (Table 4) and the evidence that sampling of the endometrial cavity was sometimes incomplete are unsatisfactory.

It is clear from our results that this technique cannot generally replace the diagnostic curettage as an investigation of endometrial pathology, and indeed its inventors did not intend that it should do so. However, there were 10 patients in this series from whom curettage produced no endometrium but an adequate Mi-Mark sample was obtained.

The Mi-Mark technique is probably not suitable for monitoring patients on hormone replacement therapy since it is unreliable in the detection of hyperplasia and early carcinoma. It could be used to screen asymptomatic at-risk populations such as postmenopausal diabetics for endometrial pathology since any positive results here would be a bonus.

The technique is also useful in the preoperative confirmation of florid endometrial carcinoma when a positive diagnosis from the Mi-Mark specimen makes curettage before hysterectomy unnecessary.

In the investigation of infertility the Mi-Mark specimen often showed that the endometrium was in the secretory phase, thus confirming that ovulation had occurred. A full curettage may be required to exclude endometritis as a cause of infertility.

A further use for the helix in rescuing the lost strings of an intrauterine contraceptive device has been documented (Husemeyer and Gordon, 1979).

Thus, although it is doubtful whether this technique is suitable for widespread screening and monitoring hormone therapy we feel that it will have uses for gynaecological outpatient investigation.

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