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ENDOMETRIAL SAMPLING TECHNIQUES IN THE DIAGNOSIS OF ABNORMAL UTERINE BLEEDING

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Endometrial sampling is a rapid, safe, and inexpensive procedure for evaluation of women with infertility or abnormal uterine bleeding. This article discusses the characteristics of endometrial sampling modalities and compares their ease of use, specificity, and sensitivity.

Multiple modalities have been developed and implemented for endometrial sampling, including abrading, lavaging, aspirating, and brushing. The use of endometrial sampling has waxed and waned since its introduction in the 1920s, but it continues to be an essential gynecologic procedure. Kelly[15] was one of the first and most aggressive proponents of endometrial sampling in an office setting, without the need for anesthesia. Subsequently, Novak et al[26, 27] and Randall[28] introduced novel instrumentation and methodologies for sampling, facilitating histologic study of the uterine lining and its pathologic states. For many years, office-based curettage with a narrow Novak curette or dilation and curettage (D&C) under general anesthesia in the operating room remained the standards for sampling of the endometrium. More recently, suction aspiration has become widely accepted as being equal to previously used techniques. Hysteroscopically directed biopsy, although more involved and time-consuming, provides the most accurate evaluation of the endometrial cavity and its pathologic states.

INDICATIONS FOR ENDOMETRIAL SAMPLING

Indications for endometrial sampling include (1) confirmation or evaluation of chronic uterine infection, acute endometritis, or tuberculosis; (2) dating of the

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endometrium for infertility evaluation; and (3) evaluation of abnormal uterine bleeding in women who are premenopausal, postmenopausal, or making use of hormonal therapy.

It is widely accepted that the postmenopausal woman with unexplained uterine bleeding should undergo endometrial sampling. Irregular bleeding in a woman younger than 45 years old is often anovulatory bleeding and necessitates endometrial sampling only if it is persistent. Perimenopausal or postmenopausal women generally require more aggressive diagnostic intervention, including endometrial sampling. This article specifically focuses on endometrial sampling modalities used in the diagnosis of abnormal uterine bleeding.

CONTRAINDICATIONS

Contraindications to endometrial sampling are few. One such absolute contraindication is pregnancy. Endometrial sampling of fertile patients after day 14 to 15 of the menstrual cycle remains controversial for fear of possibly disrupting an early pregnancy. Sampling is frequently performed during the late secretory phase of the menstrual cycle in infertile women for the purpose of endometrial dating, however. Successful term pregnancies have been reported in women who have undergone endometrial biopsy during the luteal phase of a cycle in which they have conceived.[5] Other relative contraindications to endometrial sampling are believed to be profuse bleeding, cervicitis, endometritis, cervical cancer, and coagulopathy.

SAMPLING MODALITIES

Endometrial sampling modalities can be divided into two broad classes: cytologic and histologic. The former approach uses a sponge or brush to collect cell samples by rotating an instrument inside the uterine cavity. The latter method uses a suction mechanism to collect endometrial tissue that has been separated from the endometrial lining by abrasion or curettage. In contemporary gynecologic practice, endometrial sampling is almost always performed on an outpatient basis, usually in an office setting, and requires little or no anesthesia.

Before performing an endometrial biopsy, the procedure should be explained thoroughly to the patient. Written informed consent should be obtained and indications and potential complications adequately documented in the chart. Antibiotic prophylaxis is indicated for patients with prosthetic heart valves but is not required in patients with valvular prolapse with benign murmurs. A bimanual examination should be undertaken to ascertain the position and size of the uterus. To minimize intrauterine and postprocedural cramping, a nonsteroidal anti-inflammatory agent can be administered 1 hour before the procedure. In cases in which excessive patient discomfort is anticipated or in cases of cervical stenosis, paracervical block anesthesia can be used. The ectocervix should be cleansed with an antiseptic solution (i.e., Betadine or Hibiclens) before passing any instrument into the uterine cavity.

Placement of a single tooth tenaculum on the anterior cervical lip is sometimes necessary to immobilize the cervix and provide countertraction during insertion of the biopsy instrument. Sounding of the uterus before performing the biopsy may help minimize the likelihood of uterine perforation. A calibrated aspiration catheter allows both sounding and biopsy of the uterine cavity with

the use of a single instrument. Continuous verbal communication and using gentle technique allow patients to tolerate better this quick diagnostic procedure.

COMPLICATIONS

Serious complications of endometrial sampling are rare. The most common complication is uterine perforation, with a reported incidence of 1 to 2/1000 procedures.[6] Uterine perforation may result in intraabdominal bleeding and possible injury to the omentum and intraabdominal organs. Cases of uterine perforation must be evaluated on an individual basis and management decisions made accordingly. A high degree of suspicion dramatically reduces the serious consequences that result from an undetected perforation. Should concern exist about injury to intraabdominal viscera, laparoscopic evaluation should be undertaken. Should internal bleeding or damage to internal organs be discovered, laparotomy may be indicated for surgical correction. The extent of damage secondary to uterine perforation varies with the instrument used. Narrow-diameter and blunt instruments may cause less damage, whereas rigid, sharp devices have greater destructive potential.

Patient complaints of pain and cramping during endometrial sampling vary greatly. Pain scoring is often used in an attempt to objectify the subjective nature of pain. Devices of smaller diameter and softer composition, such as the Pipelle (Unimar), and instrumentation without serrated scraping edges cause less discomfort to the patient.[13, 21, 32, 35]

Other potential complications are vasovagal reactions, bleeding, and infection. Patient complaints of lightheadedness and dizziness are reflective of hypotension and bradycardia seen with stimulation of the vagus nerve. Stimulation of the parasympathetic nervous system occurs in response to instrumentation of the uterine cavity. Resolution without treatment is usually prompt. Should symptoms persist, atropine administered intravenously quickly aborts the symptoms. Vasovagal reactions are believed to occur less frequently when paracervical block is administered before the procedure.

Significant bleeding is rarely encountered during or after an uncomplicated endometrial sampling. Continued or profuse bleeding should cause one to consider the possibility of uterine perforation. Further investigation should be undertaken, as discussed earlier. If sterile procedure is used, postprocedural uterine infection is extremely rare. Antibiotics are not necessary before or after an uncomplicated endometrial biopsy.

SAMPLING MODALITIES

Endometrial Cytologic Sampling

Many devices have been developed for endometrial cytology sampling, including the Endocyte brush, Mimark helix, Zelsmyr cytobrush, Isaacs sampler, and the Kuper brush. Cytologic samplers are designed for collection of cells that are placed in Bovin's solution, rather than formalin, so as to preserve the cytonuclear characteristics.

Devices for cytologic sampling are generally more supple and narrower in diameter than endometrial tissue suction catheters. This characteristic, along with the decreased need for grasping the cervix with a tenaculum, provides for minimal patient discomfort. These advantages are reflected in the increased

patient compliance and willingness to return for additional or repeat cytologic screening, as opposed to patients in whom more rigid aspiration biopsy catheters are used. Ferenczy et al[8] found that 100% of patients undergoing cytologic evaluation returned for subsequent biopsy compared with only 40% of patients who underwent biopsy with aspiration catheters.

Despite excellent patient tolerance to these devices, they have not been adopted widely by most practicing gynecologists. This is likely explained by the frequency in which specimens fail to yield enough tissue for reliable cytologic evaluation and diagnosis. Some sources report inadequate samples in 16% of procedures. Additional disadvantages of endometrial cytologic screening include greatly decreased sensitivity and specificity.[1, 2, 10]

Endometrial Tissue Sampling

The second class of endometrial biopsy instruments includes those that use abrasion or curettage with or without suction. Included in this class are the Novak curette (Milex, Chicago, IL), Randall curette, Tis-u-Trap (Milex), Vabra aspirator (Berkeley Medidevices, Berkeley, CA), Accurette (Axcan), Gynosampler, Endocell, Explora (Milex), Z-sampler (Zinnanti), Gynoscann, and Endosampler.

Modern endometrial biopsy suction cannulas are approximately 3 mm in outside diameter, hollow, and composed of polypropylene and have adequate tensile strength to allow for the applied force often necessary to pass the internal os. Suction cannulas generally have a cell collection port on the lateral aspect of the tip that is continuous with the hollow center of the suction cannula. An internal plunger extends the full length of the suction cannula, which, when retracted, creates a vacuum of sufficient strength to draw endometrial cells and tissue through the collection port.[35]

The procedure is accomplished by passing the suction cannula through the cervix until the fundus is reached. Without further advance, vacuum suction within the cannula is created, and the specimen is collected while the cannula is removed slowly from the uterine cavity. Spiraling rotations of the suction cannula between the thumb and index finger during the withdrawal process allow for a more generous specimen. Multiple passes of the suction catheter may be necessary to collect an adequate sample. The specimen is preserved in formalin and transported in a sealed container to pathology.

Evolution of Endometrial Sampling

Before describing the unique characteristics of endometrial sampling devices, a brief narrative regarding their evolution follows. D&C was, for many years, the gold standard of endometrial sampling. Introduced by Recamier in 1843 to "scrape off uterine fungosities," the D&C has a significant following more than a century later. Despite its long-standing and continued use, many questions exist regarding its tissue yield and diagnostic accuracy.[12]

In 1925, Kelly[15] described a procedure that could be accomplished without anesthesia on the office examination table. A spatula rotated inside the uterine cavity harvested endometrial cells. In 1935, Novak[26] introduced a novel thinner curette, which could be introduced more easily into the uterine cavity without cervical dilation. The Novak curette was intended to be used as a method for sampling of the endometrial cavity in the office with little or no anesthesia.

Shortly thereafter, the Randall curette, a modification of the Novak curette, was introduced.[28] With a single tooth in place of the Novak curette's serrated edge, it yielded adequate tissue specimen while causing less pain.

For many years, the D&C and the endometrial biopsy using a curette were gynecologic mainstays. In the United States in 1975, approximately 835,000 surgeries listed D&C as the first procedure. In 1977, the number had increased to 977,000.

The number of D&Cs performed continued unabated until the early 1980s, when Grimes[12] published an extensive literature review. He noted that D&C carried a higher risk of perforation, infection, and bleeding and was more expensive than other endometrial aspiration technologies available at the time. Worse yet, D&C specimens offered no greater reliability. He cautioned that "Until the purported benefits of diagnostic D&C can be shown to be worth its risks, inconvenience and cost, the procedure should probably not be the primary method of obtaining samples of endometrium from most patients."[12]

Grimes found that disposable catheter-type instruments with mechanical suction for collecting endometrial specimens produced specimens with equal diagnostic accuracy as D&C. In the years since Grimes' article, suction aspiration catheters that offer more convenience and use only manually generated suction have been developed and provide adequate specimens for histologic evaluation equal to those that require mechanical suction.

In the late 1980s and early 1990s, several articles appeared that demonstrated that hysteroscopy with directed biopsy provided unparalleled specificity and sensitivity in detecting pathologic states of the endometrium.

Specific Endometrial Biopsy Technologies

The Novak curette, the best known of the early endometrial sampling devices, remains a standard to which many newer technologies are compared (Table 1). As originally described, the Novak curette was a rigid, reusable stainless steel cannula 25 cm in length with an outer diameter of 4.2 mm and an inner diameter of 3.2 mm.[18] Serrated edges surrounded an aperture measuring 1 cm by 3.2 mm that opened 3 mm from the distal end. At the noncutting end of the curette was a Luer-Lok that allowed attachment of a 10- or 20-mL plastic syringe. The endometrial sample was drawn into the cannula and syringe by creating a negative pressure by withdrawing the syringe plunger. To accommodate different sized cervices, the modern Novak curette is currently available in sizes that range from 1 to 4 mm.

The Randall curette, a modification of the Novak curette, is also made of

Table 1. COMPARISON OF ENDOMETRIAL SAMPLERS

	Manufacturer	Inner Diameter (mm)	Outer Diameter (mm)	Reusable
Novak Curette	Milex	3.2	4.2	yes
Randall Curette	Cooper	3.2	4.2	yes
Vabra Aspirator	Berkeley	3.2	4.2	yes
Tis-u-Trap	Milex	1.8–4	2–4	no
Accurette	Axcan	3.2	4	no
Pipelle	Unimar	2.6	3.1	no
Explora	Milex	2.6	3	no
Z-sampler	Zinnanti	2.6	3.1	no

stainless steel. Instead of a serrated edge, this device has a large, single tooth at the distal opening. Both the Novak and Randall curettes have rounded noses and slightly curved tips to facilitate navigation through the endocervical canal.

The Vabra aspirator is a 3-mm diameter stainless steel suction cannula to which an electric suction pump is attached to facilitate collection of the sample. The Vabra aspirator has a reservoir trap for sample collection on the proximal end of the shaft. Used in conjunction with an electrical suction pump, pressures of 500 to 600 mm Hg are generated within the uterus to enable extensive sampling of the endometrium in less than 1 minute.[27] Initially embraced by practitioners who had made use of the Novak and Randall curettes, the Vabra aspirator's popularity has waned over the past several years as newer, disposable, and flexible endometrial sampling devices have emerged.

The Tis-u-Trap was designed to be an all-in-one curette, tissue filter, and specimen container that, like the Vabra, uses an electric suction pump. After endometrial aspiration is accomplished, formalin is added to the specimen container, which is sent to the laboratory. Curette tips are available in flexible or rigid plastic and in varying diameters, although the most commonly used device is 4 mm. The applicability and practicality of this technology is limited by the need for a suction pump, the noise of which often intimidates patients.[16]

In evaluating the value of various sampling modalities, a comparison must be made of the percentage of specimens that yield adequate tissue to allow histologic diagnosis. An additional critical characteristic of any device is its accuracy (i.e., sensitivity and specificity).

Studies continue to denigrate the D&C by documenting that this technique samples less than 75% of the uterine cavity in 84% of patients and less than 50% of the uterine cavity in 60% of patients.[29, 34] Additional studies have shown that 4% to 20% of D&Cs yield specimens with inadequate tissue for histologic diagnosis, because abraded strands of endometrium often are not evacuated from the uterus and submucosal fibroids and polyps almost always are not sampled. As many as 10% to 35% of endometrial lesions may be missed because the D&C is a blind procedure and lacks a reliable way to retrieve material after it is separated from the endometrial lining.[20]

Newer technologies such as Vabra and Tis-u-Trap have revealed diagnostic capabilities equal to that of the D&C and the Novak curette. Vabra has been found to produce adequate specimens in 94% of cases and Tis-u-Trap in 84%. Their sensitivities in disease detection are 83% and 92%, respectively. Tissue adequacy as well as sensitivity of pathology detection with each have been proved equal to that of the Novak curette and better than the D&C. Additional benefits are increased patient comfort and savings in time and cost.

In the last several years a streamlined Pipelle-type suction aspiration cannula has become available. It is innovative because it does not require an external electric suction pump, which allows for a quicker and less expensive procedure characterized by less patient discomfort.[3, 31] Many studies have compared the Pipelle with the Novak, Vabra, Tis-u-Trap, and D&C. Stoval et al[37] found samples taken with the Novak and Pipelle curettes to be comparable: 90.8% versus 87.2%, respectively. The Vabra aspirator and the Pipelle were found to be essentially identical (94% and 95%, respectively) in producing specimens adequate for diagnosis.[22] Koonings et al[16] compared the Pipelle and the Tis-u-Trap. The sampling devices were comparable in obtaining adequate specimens, with Pipelle at 88% and Tis-u-Trap at 84%. Table 2 summarizes studies that have examined the adequacy of endometrial biopsy sampling. Studies conducted to compare the effectiveness of the Pipelle to the Vabra aspirator found that both devices obtain adequate specimens: 98.7% and 94.9%, respectively. Pathologic

Table 2. ADEQUACY OF ENDOMETRIAL BIOPSY SAMPLE

Device	Premenopausal (%)	Postmenopausal (%)
Tis-u-Trap	84	
Pipelle	87–97	78
Novak	90–96	72–76
Z-sampler	95	74
Vabra	94	

diagnoses between samples obtained by both methods on the same patient, on the same visit, agreed in 94% of cases, which leads to the conclusion that the two methods have equal diagnostic accuracy.[22]

Rodriguez et al[29] compared samples obtained with the Pipelle and the Vabra aspirator in women just before undergoing hysterectomy. They found that the Pipelle sampled only 4% of the endometrial lining compared to 41% with the Vabra. Dividing the uterus into eight quadrants (four anterior and four posterior), Rodriguez et al found that only 2.4 quadrants were sampled with the Pipelle compared to 7.4 with Vabra.[29] The Pipelle biopsy, however, agreed with the posthysterectomy diagnosis in 84% of cases, allowing the conclusion that the diagnostic accuracy of the two procedures is equal.

In cases of suspected endometrial carcinoma, sampling devices must be most reliable. In a review of 14 studies, the sensitivity for cancer detection with Vabra aspirator was found to be 93% and the sensitivity for detection of hyperplasia was 95%. With Pipelle use, the sensitivity was found to be 90% for cancer detection and a range of 83% to 90% for hyperplasia detection (Table 3).

Table 3. SUMMARY OF SENSITIVITIES AND SPECIFICITIES OF ENDOMETRIAL SAMPLING DEVICES

Device	Sensitivity (%)	Specificity (%)
Pipelle[38]	44.6–51 (D) 100 (C)	98.5 (D) 99.1 (C)
D&C	65	100
Pipelle[14]	83 (C)	—
Pipelle[37]	97.5 (C)	—
Pipelle[29]	84.6 (D)	—
Z-sampler[18]	94.5 (D)	—
Vabra[29]	83.3 (D)	—
D&C[41]	90 (D)	—
Tis-u-Trap[16]	92 (D)	—
Transvaginal sonography	82	80
Saline infusion sonography	100	80
Hysteroscopy	97–98	93–100

D = disease other than invasive carcinoma; C = carcinoma.
Data from references 20, 38, 39, 40.

HYSTEROSCOPY

Studies conducted to assess the effectiveness of hysteroscopy with directed biopsy have shown a sensitivity of 97% to 98% and a specificity of 93% to 100%.[19, 38] In 1984, Gimpelson and Rappold[9] studied 66 women with hysteroscopy before a planned D&C. In 16 patients, hysteroscopy with directed biopsy revealed more information than a D&C would have alone. The efficiency of D&C compared to hysteroscopy was investigated further by Gimpelson and Rappold in 1988. In 342 women symptomatic for abnormal uterine bleeding, D&C was performed followed by hysteroscopy with directed biopsy. In 60 women, the correct diagnosis was missed by D&C but made with hysteroscopy and directed biopsy.[9]

SUMMARY

There have been many advances in sampling of the endometrium. Ideas and technologies have evolved, increasing our ability to gather adequate specimens that provide reliable information about uterine cavity pathologies. No technique surpasses the sensitivity and specificity of hysteroscopy with directed biopsy. Owing to its superior diagnostic potential, hysteroscopy, even when performed in the office with narrow scopes (not significantly larger in diameter than the Pipelle catheter), leads to precise diagnosis and appropriate management of intrauterine pathologic conditions. For physicians who are untrained or lacking the equipment to perform diagnostic hysteroscopy with directed biopsy, simple in-office endometrial sampling techniques with no visual control provide a means to obtain reasonably reliable samples with negligible patient discomfort.

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