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Endometrial Biopsy

A Review of Sampling Technique

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Introduction

Abnormal uterine bleeding (AUB) is responsible for 33% of all outpatient gynecologic visits, with the majority of cases just after menarche or in the perimenopausal period.[1] Most cases are related to pregnancy, anatomic uterine pathology (fibroids, polyps, adenomyosis), anovulation, maladies of hemostasis, or neoplasia. Since evaluation of the endometrium is a key component in the diagnostic triage of women with AUB, clinicians must be aware of the diagnostic capabilities of available techniques.

Numerous studies have shown that the endometrium is adequately evaluated with office sampling techniques. It is important to remember that all sampling devices perform better when pathology is global rather than focal. Excellent correlation exists between the histopathology of endometrial specimens taken by biopsy instruments in the office and D&C.[2] The sampling portion of an endometrial biopsy can usually be performed in less than 15 seconds; thus, most patients tolerate the procedure well with the use of non-steroidal anti-inflammatory agents 1 hour prior to the office visit.

Recently, interest has been shown in adapting the elements of cytology to sampling of the endometrium, utilizing an endometrial brush along with proprietary laboratory processing (Tao Brush™ Gynecor, Tru Test™ Cook® Medical). Clinicians should be cognizant of important differences in this technique and the resultant specimen obtained, as compared to the Pipelle® device, which is widely regarded as the most popular method for sampling the endometrial lining.[3]

Sampling Techniques

Pipelle®

The Pipelle is constructed of flexible polypropylene with an outer sheath measuring 3.1 mm in diameter with a 2.4 mm distal side port, through which the endometrial sample is obtained. Its flexibility allows the cannula to conform to the contour of the uterus and minimizes cramping. Most often, the Pipelle can be inserted without the aid of a tenaculum. Once placed within the uterus, the clinician stabilizes the sheath with one hand and pulls the piston out as far as possible to create suction. The sheath is rotated 360 degrees while withdrawing the distal port from the fundus to the internal os, with multiple passes being performed as necessary. The specimen is expelled into the formalin container by pushing the piston into the sheath. If there appears to be insufficient tissue for diagnosis, a second pass of the catheter is performed using the same catheter if it has not touched the formalin. At the conclusion of the procedure, the tip of the catheter containing the specimen can be cut off and dropped into the formalin.

The Pipelle sample consists of tissue fragments that are aspirated from the uterine cavity. The specimen is submitted for evaluation in 10% neutral buffered formalin (the routine fixative for most histology specimens). The pathology laboratory personnel describe the specimen grossly, filter the specimen to collect the tissue fragments and discard the fluid.

Gynecor TruTest utilizing the Tao Brush

The TruTest utilizes the Tao Brush (TB) for obtaining a sample from the endometrium by inserting it into the uterine cavity, and like an endocervical brush, scraping the uterine walls. The Tao Brush cut-end is placed in a fixative vial and must then be mailed to the Gynecor lab for processing. The TB specimen consists of the brush tip submitted in a fixative that is routinely used for liquid-based cytology preparations. The submitted sample is filtered if gross tissue fragments are visualized, and the fluid is centrifuged to make a tissue-dense button. This may yield two samples: (1) a tissue block, processed in 10% formalin, which generates an histology slide, and (2) cytology smears prepared from the centrifuged liquid, akin to that for liquid-based cytology used for cervical cancer screening.

While claims that the TB is gentle and minimizes the risk of uterine injury and pain, the literature is mixed. For example, in Marksem's 2000 *Diagnostic Cytopathology* paper, 113 patients were allocated for Tao sampling. In 11 cases, clinicians reported a failure to pass the brush into the endometrial cavity, noting that the women complained of pain.[4]

At the microscope, the Pipelle biopsy appears as a tubular fragment that can be several millimeters in length and about 1.5 millimeters wide. The TB histologic specimen is described as a micro-biopsy: a collection of non-confluent tissue.[5] The sample size is larger for the Pipelle as compared to the TB, and also appears to have tissue from deeper segments of the endometrium. The cytologic endometrial sample is obtained only with a TB specimen and allows for the evaluation of the endometrium cytologically. This is often the only sample in a postmenopausal woman. If enough material is available, both specimens are amenable to immuno-histochemistry.

Product Performance

The American Cancer Society suggests that women at average or increased risk of developing endometrial cancer be informed about their risks of developing the disease, educated about its symptoms (unexpected bleeding) at the onset of menopause, and strongly encouraged to report such symptoms to their health care provider promptly. Screening asymptomatic women for endometrial cancer is generally not warranted, except those with Hereditary Nonpolyposis Colon Cancer (HNPCC). Since endometrial cancer commonly causes abnormal uterine bleeding, most cases will be detected early without screening (72% percent of women with endometrial cancer are diagnosed while in stage I).[6] Table 1[7] highlights which patients should undergo evaluation for endometrial hyperplasia or endometrial cancer.

Table 1: Women who should undergo evaluation for endometrial hyperplasia or endometrial cancer:

- Over age 40 years with AUB
- Under age 40 with AUB and risk factors (e.g. chronic anovulation, obesity, using tamoxifen, diabetes, family history of endometrial, ovarian, breast or colon cancer
- Failure to respond to medical treatment of AUB
- Women with uterus in situ receiving unopposed estrogen replacement therapy
- Presence of atypical glandular cells on cervical cytology
- Presence of endometrial cells on cervical cytology in a woman 40 years or older
- Women with hereditary nonpolyposis colorectal cancer

In the process of obtaining a sample, it is important to understand the differences and limitations of the respective collection and processing procedures. While a patient with an atrophic endometrium may pose difficulty in obtaining a sample with a conventional biopsy instrument, the utilization of cytology and a "microbiopsy" specimen poses several limitations on interpretation and clinical management:

Diagnosis of atypical hyperplasia/carcinoma and the volume/depth of the sample and the evaluation of atypia.

The diagnosis of hyperplasia has a very high rate of disagreement amongst pathologists. Recent literature suggests that there is this greater disagreement on diagnosis if the volume of tissue or the volume of lesion is low.[8] In addition to the TB microbiopsy sample being smaller than a Pipelle sample, it is not representative of a confluent specimen. To augment the TB endometrial microbiopsy histology, the TruTest system utilizes cytologic atypia as one of the backbones for the diagnosis of atypical hyperplasia and carcinoma. The gynecologist must be aware that cytologic atypia is the single criterion where there is the maximal inter and intra-observer variation in the diagnosis of hyperplasia/carcinoma.[8] Additionally, about 1/3 of well-differentiated endometrial carcinomas show little or no nuclear atypia and the pathologist must fall back on architecture to diagnose carcinoma. Architecture is obviously more easily appreciated on a larger fragment of tissue rather than a smaller fragment of tissue. In the past this likely did not have significant ramifications. However, with the recent National Comprehensive Cancer Network guidelines that recommend all endometrial carcinomas (including Grade 1) be fully staged, the line of demarcation (for staging) has shifted from low-grade and high-grade carcinoma to atypical hyperplasia and carcinoma.

Statistics

Both the Pipelle and TB obtain an adequate sample in premenopausal women, however, for postmenopausal women, the Tao Brush may yield a higher rate of reported adequacy. It is the cytology smear, with all the limitations noted above, that accounts for the difference in postmenopausal women, as they have atrophic uteri and therefore very little tissue to sample via suction.

Initial studies (with a limited number of patients) utilizing the TB noted 95.5% sensitivity, 100% specificity, 100% positive predictive value and 98% negative predictive value.[9] However, the most recent cumulative data (1,543 cases) provides an updated analysis of the TB performance from a larger patient population - sensitivity of 88%, specificity of 92%, positive predictive value of 79%, and a negative predictive value of 95%. Some highlights from the most recent substantial paper:[10]

- With the use of the TB/endometrial cytology, 11.6% of endometrial neoplasms (atypical hyperplasia or worse) were called benign abnormality. Two of these were overt carcinoma, although the stage of the tumor or the grade of the tumor is not stated. Eighteen percent of a typical hyperplasias were called benign. This has led the authors to suggest that the diagnosis of "benign abnormality" be followed further to avoid missing a more serious diagnosis. This would mean that 30% of adequate samples would need additional evaluation in the form of a "real biopsy."

- Positive predictive value of 79% indicates a significant risk that some of the cases will be diagnosed by this technique as carcinoma, but will eventually be proven to be benign. Since it is very difficult to prove that a patient does not have carcinoma, the only way to proceed maybe to remove the uterus and entirely embed and examine histologically to rule out the presence of carcinoma (which is what was done in this study). Therefore, from the pathologists point of view, it is suggested that the results of a Tao Brush sample be reported as a risk stratification:

  i. Benign - virtually no risk of cancer - no additional studies required.

  ii. Benign abnormality - intermediate risk for cancer, additional studies required

  iii. Precancer/Cancer - high risk of cancer, however benignancy can not be excluded. Additional studies required.

This reporting strategy may work for a screening test, but would require that the clinician bring 30% of their patients back for further evaluation. Some of these patients will require an extensive work-up because of a working diagnosis of very high risk for carcinoma, and possibly may require a hysterectomy to rule out the possibility of carcinoma.

As Pipelle has been utilized extensively for endometrial biopsy for some time, a large body of literature is available for review (a sample of the literature):

- Published in 2000 by the American Cancer Society in their journal *Cancer*, the accuracy of endometrial sampling was studied in the diagnosis of patients with endometrial carcinoma and hyperplasia. The published data, which included four separate studies in meta-analysis format in a postmenopausal population, the sensitivity of the Pipelle for diagnosing endometrial cancer was 99.6%. They concluded based on 39 studies with 7,914 women, endometrial biopsy with the Pipelle is superior to other endometrial techniques in the detection of endometrial carcinoma and atypical hyperplasia.[11]

- A 2003 study that compared the specimen obtained by Pipelle in 628 patients with AUB. Of these patients, 249 underwent transcervical resection of the endometrium (TCRE) and 75 had a hysterectomy within six months. Comparing the two subgroups 'malignant' and 'benign', the positive predictive value for endometrial malignancy was 100% (95% CI, 73.5–100). Insufficient tissue was obtained in five cases (1.5%).[12]

- A 2007 publication illustrating Pipelle performance in 360 patients with endometrial cancer published in *AJOG* - the sensitivity of Pipelle was 93.8% in patients with low-grade cancer and 99.2% in patients with high-grade cancer along with a positive predictive value of 94.6%.[13]

- A 2008 publication compared endometrial sampling by Pipelle endometrial curette with conventional dilatation and curettage (D&C) in patients with abnormal uterine bleeding. An adequate sample was obtained in 98% of cases by Pipelle and in 100% of cases by D&C. Pipelle had a sensitivity, specificity, positive predictive value and negative predictive value of 100% for diagnosing endometrial carcinoma, hyperplasia and secretory endometrium. Pipelle had a diagnostic sensitivity, specificity and negative predictive value (100%, 98% and 100%, respectively) for hyperplasia with atypia.[14]

Concerning the Pathologist

Significant contrast exists between the interpretation and reporting of specimens obtained by the Pipelle and examined by the local pathologist, and those obtained with the TB and submitted for TruTest processing:

- Standard processing and interpretation is performed on histologic specimens obtained with the Pipelle device. For the TB, reference laboratory (Gynecor) pathologists use EIN (endometrial intraepithelial neoplasia), which, although an approved alternative to the WHO classification system, is not widely used. This system is based on solid molecular and genetic evidence to describe the pre-cancerous lesion of endometrioid endometrial cancer. It includes the vast majority of atypical hyperplasias and some percentage of complex hyperplasias. The criteria needed to make this diagnosis are: the size of the proliferation exceed 1mm in size; the lesion be cytologically different from surrounding endometrium and that mimics such as polyps be excluded.[15] In publications describing the TruTest technique, authors state they use this classification; however, they insert that the nuclei have features of grade 2-3 carcinoma. This modification is not a criterion for the diagnosis of EIN. Leading to a certain amount of confusion, the new term of "cytological EIN" has been proposed without clear management guidelines. With the traditional use of the EIN terminology, a patient diagnosed with EIN is at a 45-fold increase for developing endometrial carcinoma.[16] In most cases, patients with this diagnosis should be treated as having at least atypical endometrial hyperplasia. With the use of the cytological EIN terminology, the clinician would have to perform a hysterectomy (it is impossible to exclude the presence of carcinoma without removal and examination of the uterus) to rule-out disease.

- The proprietary nature of the TB/TruTest also presents several obstacles. The traditional approach with a pathology laboratory allows for extensive communication between pathologist and gynecologist. Many institutions review all cancers in a "tumor board" session that facilitates all parties to review the histology and plan the optimal treatment regimen. A proprietary lab would need to forward slides to the treating institution for review and comparison with the surgical specimen. Should the "host" pathologist disagree with the TruTest diagnosis or be unconvinced of the value of micro-biopsy or the use of cytological EIN, a repeat traditional histology biopsy may be recommended.

Summary

Abnormal uterine bleeding can be caused by a wide variety of local and systemic disease or even be related to pharmaceuticals. All women with abnormal uterine bleeding should have a complete history and physical examination. Information should be obtained on the frequency, duration, and volume of abnormal uterine bleeding, as well as the presence of associated symptoms and precipitating factors. Diagnostic endometrial sampling is preferable to D&C because it is more convenient, less expensive, safer and equally reliable, but does not typically require cervical dilation, hospitalization or general/regional anesthesia. All endometrial sampling devices perform better when pathology is global rather than focal.

Gynecologists must be aware of new techniques in endometrial sampling as well as their performance characteristics compared to current standard of care devices. While the novelty of the TueTest utilizing the TB is intriguing, it is important to be aware of the limitations of its diagnostic capability. The current literature would support the Pipelle as the "gold-standard" in endometrial samplers.

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