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Methods of Endometrial Evaluation

Endometrial Sampling Techniques

There are several methods of sampling the endometrium. The "gold standard" is dilation and curettage (D&C), which requires dilation of the cervix to allow insertion of a curette into the endometrial cavity.[1–5] This technique allows for the most thorough sampling of the endometrium but requires anesthesia for cervical dilation. The curette is drawn across the anterior and posterior endometrial surfaces, scraping the tissue free. D&C also readily allows for a fractional curettage with sampling of both the endometrial and the endocervical mucosa. Fractional sampling is especially useful for evaluating possible endocervical pathology, such as extension of endometrial adenocarcinoma to the endocervix.[6] D&C is most commonly used in situations in which more extensive sampling of the endometrium is needed to exclude significant pathology or to remove as much endometrium as possible in patients with severe abnormal endometrial bleeding.[1–5;7–11]

Complications of D&C can include hemorrhage, infection, or perforation, although each of these appears to occur at a rate of between 4 and 6 per 1000 procedures.[1;12] Because many patients who undergo D&C do not come to hysterectomy, the overall sensitivity and specificity of this technique have been difficult to determine. Several studies found that D&C missed a significant number of polyps, hyperplasias, and carcinomas.[13–15] In fact, one study found that D&C performed immediately before hysterectomy often sampled less than half of the cavity, suggesting that this procedure may fail to fully document significant endometrial pathology.[13] Curettage or biopsy before hysterectomy for leiomyomas also has little value, rarely identifying a significant lesion,[16] although patients with leiomyoma and abnormal bleeding may rarely have a malignancy.[17] Several investigators also have found discrepancies between the grade of endometrial carcinoma in curettage specimens as compared to hysterectomy specimens.[9;11;18–21]

Strictly applied, the term "endometrial biopsy" refers to a limited sampling procedure that does not require endocervical dilation prior to sampling. Endometrial biopsy is relatively painless and does not require the anesthetic used for D&C. It is usually an office-based procedure.[3–5;22] These samples are taken either with a small sharp curette, such as the Novak or Randall curette, or with a flexible plastic cannula that uses suction to aspirate

the tissue. The Pipelle endometrial aspirator (Cooper Surgical, Shelton, CT) is the most widely used of these devices. Limited sampling techniques are especially useful for obtaining smaller specimens for endometrial dating in infertility patients or for evaluating the response of endometrial tissue to steroid hormone therapy of various types. Hyperplasia and neoplasia can be accurately diagnosed by the endometrial biopsy, however,[23–28] and it is possible to perform limited fractional sampling of endocervical as well as endometrial tissue using some biopsy devices. Because these various biopsy procedures can be done in the office rather than the operating room and because they yield sufficient specimens for diagnosis in most cases, they are cost-effective methods for endometrial evaluation.[1;2;22]

The Pipelle and related devices have received widespread clinical usage because they are simple to use, cost effective, and reliable for giving adequate tissue samples in most cases.[12] The Pipelle-type device uses a handheld piston to generate negative pressure and aspirate tissue through a narrow cannula inserted into the endometrial cavity. The Pipelle does change the pattern of tissue fragmentation, yielding cylinders of tissue with small portions of endometrium mixed with fresh blood clot. Comparisons of the Pipelle sampling device with other, more traditional, sampling mechanisms show no significant difference in the overall quality of tissue taken for evaluation,[28–39] although some studies find that the Pipelle technique samples much less of the endometrial surface than other biopsy devices.[37] Limited sampling with these devices may lead to some under diagnosis of significant abnormalities, however.[25;27;40–42] The Pipelle also has limited sensitivity for detecting intrauterine gestation and excluding an ectopic pregnancy.[40]

Other aspiration devices, such as the Vabra aspirator (Berkeley Medevices, Berkeley, CA) or the Tis-U-Trap (Milex Products, Chicago, IL), use a mechanical vacuum to extract tissue into a tissue collection apparatus.[1;22;29;30;37;43] The cannula for these devices is thin, ranging from 3 to 4 mm, so general anesthesia is not required. This technique tends to result in extensive fragmentation of the tissue, but the overall quality is comparable to that of a D&C specimen for diagnosis. Another advantage of this method is that it samples much of the endometrium. Endometrial brush biopsy using the Tao Brush (Cook OB/GYN, Bloomington, IN) also has been effective in detecting endometrial abnormalities.[44;45] This technique uses a brush to remove tissue for both histology and cytology, and requires a special fixative and centrifugation to prepare the material.

An aspiration technique called suction curettage is used in evacuating early (first trimester) abortion specimens. The procedure requires cervical dilation and is often done under local anesthesia (paracervical block), as general anesthesia increases the risk of perforation, visceral injury, and hemorrhage during extraction of the aborted gestation.[46;47] In very early pregnancy, however, endometrial aspiration, which is often termed "menstrual extraction," can be performed using a small plastic cannula without anesthesia or dilation. After the first trimester, but generally before the 20th week, abortion can be performed by dilation and evacuation (D&E), a technique that employs gradual cervical dilation using an osmotic dilator (*Laminaria japonica*).[46;47]

Noninvasive Methods of Endometrial Evaluation

Hysteroscopy

Hysteroscopy with fiberoptic illumination is widely used for visualizing the endometrium and allowing directed biopsy or excision of lesions.[3;48–50] Hysteroscopy, especially with a large-diameter hysteroscope, may require local or general anesthesia, and in some patients cervical dilation is necessary. With small-diameter scopes, this can be an office-based procedure, however. The technique is usually performed by distending the endometrial cavity to allow visualization, a procedure termed "panoramic hysteroscopy."[3;51] For the larger scopes the distending medium often is dextran, although other substances, such as 5% dextrose and water and carbon dioxide gas, may be used. A nondistending technique known as "contact hysteroscopy" does not require a distending medium. In this technique the surface to be

viewed is touched, and lesions are identified by their contour, color, vascular pattern, and spatial relationships.[3;52]

Hysteroscopy has the advantage of giving directed biopsy specimens, in contrast to the blind biopsy offered by other procedures. It is useful for evaluation of women with abnormal uterine bleeding. It can reveal polyps or small submucosal leiomyomas and enhances clinicopathologic correlations. The technique is useful before and after D&C to make certain that lesions such as polyps or adhesions are removed by the curettage. In fact, hysteroscopy with endometrial resection may provide superior detection of focal endometrial lesions compared to D&C alone.[14] In addition, hysteroscopy can help in evaluation of women with repetitive abortions who may have a congenital abnormality, such as a septum. This procedure also can be used to determine the extent and possible cervical extension of endometrial carcinoma. The technique of hysteroscopically directed transcervical resection of the endometrium can be used as a therapy for dysfunctional uterine bleeding, obliterating the endometrium.[49;53]

Ultrasound

Transvaginal ultrasound is another adjunctive technique for examining the endometrium.[54–70] Sonography with a transvaginal probe evaluates the thickness and morphology of the endometrium. The technique permits measurement of the thickness of the combined anterior and posterior endometrium, which is referred to as the endometrial "stripe." This parameter can assist in determining pathologic and physiologic changes in the endometrium.[55;61] In postmenopausal patients a thin endometrial stripe of less than 4 or 5 mm indicates that a significant pathologic lesion of the endometrium is unlikely,[58;71] whereas a stripe thicker than 5 mm suggests the presence of polyps, hyperplasia, or carcinoma. In addition, this procedure can help to determine the presence or absence of myometrial invasion by endometrial carcinoma. Ultrasonography also is useful for determining the degree of development of the endometrium in the secretory phase by determining its thickness and texture.[54–57] This technique cannot replace biopsy for accurate evaluation of endometrial morphology, however.[60]

Both transvaginal and transabdominal ultrasound are useful for assessing the possible presence of an ectopic pregnancy. When ectopic pregnancy is suspected, sonography can determine whether a gestation is in utero or tubal.[72] Both methods of ultrasound also are used in the diagnosis of gestational trophoblastic disease, especially hydatidiform mole.[73]

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) provides a clear view of the uterine anatomy that is especially useful in the evaluation of tumors.[3;74–79] MRI demonstrates the endometrial–myometrial interface or "junctional zone," so it can be used to assess myometrial invasion by endometrial carcinoma.[80] It also can demonstrate myometrial invasion in gestational trophoblastic disease.[81] On occasion this technique is useful for careful follow-up or assessment of other forms of uterine neoplasia, such as stromal tumors or leiomyomas. MRI is time consuming and expensive, however, and it is not practical for routine evaluation of nonneoplastic conditions.

Histologic Techniques

Gross examination of endometrial tissue is generally not reliable for selecting material for microscopy. Consequently, in most cases, the whole tissue specimen should be submitted. For abortion specimens containing abundant tissue, three cassettes are sufficient to verify the presence of placental tissue (chorionic villi or trophoblast). If gross examination shows placental tissue, however, one cassette will be sufficient if the study is intended only to document the presence of an intrauterine gestation. An exception is examination of hydatidiform mole. A minimum of four tissue blocks should be submitted to ensure adequate assessment of the chorionic villi, including the degree of trophoblastic hyperplasia and atypia.

Proper technique is requisite to ensure adequate histologic evaluation. Biopsy tissue that suffers from suboptimal fixation, processing, or

sectioning will have artifacts that hinder microscopic evaluation. Fixation of endometrial tissue often is difficult because of the large amount of blood that is admixed with the tissue fragments. Some pathologists advocate special fixatives such as Bouin's for endometrial biopsies, since they offer excellent cytologic detail,[82] but formalin is the most widely available and accepted fixative and, in our opinion, is the fixative of choice. Acid-containing fixatives such as Bouin's degrade DNA, limiting any type of molecular analysis of the tissues.

Before processing, tissue fragments should be separated from as much blood as possible. Well-fixed tissue can be placed in a tea strainer and briefly rinsed with water to remove some blood before placing into a cassette. Wrapping the tissue in thin, porous paper (tissue wrap or lens paper) or placing tissue in a porous "biopsy bag" or tea bag in the cassette prevents loss of small tissue fragments. Experience has shown that sponges used to hold small specimens in cassettes cause artifacts and distort the three-dimensional configuration of the tissue.[83] During processing, immersion in alcohol–formalin removes some of the blood, which aids in subsequent sectioning. Modern tissue processors using vacuum provide optimal dehydration and penetration of paraffin into tissue. In our experience, ethanol is a better dehydrating agent than denatured alcohol. To achieve optimum processing, it is necessary to change reagents in the processor daily.

Specimens from endometrial biopsies and curettings are among the more difficult tissues to section, because they are highly fragmented and bloody. The paraffin-embedded tissue tends to be dry, resulting in shatter and a "venetian blind" effect. Warming the block in warm water and then applying ice to the surface of the block facilitates even sectioning, with decreased fragmentation and shatter. Specimens should be cut at 4 to 6 μm.

The paraffin blocks should be cut at multiple levels (two or three) in most cases. Multiple levels, or step sections, are especially important for smaller samples embedded in one or two cassettes. Step sections provide the most comprehensive study of the tissue, allowing the pathologist to assess the three-dimensional aspects of the tissue, and are especially useful for endometrial samples, because the tissue tends to be highly fragmented and haphazardly oriented. Furthermore, levels on the block can uncover occasional subtle abnormalities that would not be noticed if only a single section was reviewed. For example, levels may clarify the presence of a polyp or they may reveal that an apparent polypoid structure simply represents tangential sectioning of normal endometrium. Levels also help to determine whether apparently disordered glands represent a true abnormality or are simply an artifact of the procedure. Even endometrial biopsies for histologic dating in infertility patients benefit from multiple levels; frequently the histologic date is correctly adjusted by identifying more advanced secretory changes in step sections.

Routine hematoxylin and eosin (H&E) stains generally suffice for the diagnosis of most specimens. Other histochemical stains are rarely necessary. The use of the periodic acid–Schiff (PAS) stain to demonstrate glycogen in the early secretory phase has no advantage over careful examination of routine H&E sections for subnuclear vacuoles. Biopsies showing granulomatous inflammation should be stained for acid-fast and fungal organisms. Tissue Gram stains are not useful for evaluation of most cases of endometritis. Stains for epithelial mucin, such as mucicarmine and alcian blue, are useful for establishing the diagnosis of adenocarcinoma in a poorly differentiated malignant tumor. Mucin stains have little utility for determining endometrial versus endocervical primary sites, however, because tumors at either site show variable amounts of cytoplasmic and luminal mucin (see Chapter 10).

Frozen Section

Frozen sections can be useful in the evaluation of occasional cases. Usually, however, frozen sections cause significant artifacts in endometrial tissue, as the tissue often is edematous and contains considerable blood. These tissues have very different consistency and water content

compared to other specimens, such as lymph nodes or breast tissue. Consequently, laboratories that routinely use frozen section for the latter tend to have greater difficulty obtaining sections from endometrial samples.

On occasion a frozen section is requested just prior to hysterectomy in a perimenopausal or postmenopausal woman with abnormal uterine bleeding to determine whether carcinoma is present. This technique is helpful if the tissue is clearly benign or clearly malignant. The subtleties of glandular patterns, which are crucial in distinguishing atypical hyperplasia from well-differentiated adenocarcinoma, can be substantially obscured by artifacts caused by the frozen section technique, however. A better method of assessing the endometrium preoperatively is to obtain an office-based biopsy. Formalin-fixed specimens can be rapidly processed and reported, offering greater diagnostic accuracy.

One other occasional application of frozen section is in the evaluation of the patient with a possible ectopic pregnancy. Frozen section can help establish the presence or absence of intrauterine trophoblastic tissue in selected cases. Usually, however, measurement of serum progesterone, serum β-human chorionic gonadotropin (β-hCG) measurements, and transvaginal ultrasound can be used to assess the possible presence of an ectopic gestation before resorting to curettage.[84] When curettings are obtained, an attempt should be made to visualize villi by floatation of the specimen in saline before resorting to frozen section.

Immunohistochemistry

Accurate interpretation of most endometrial biopsies depends primarily on evaluation of well-fixed and carefully prepared H&E sections. In an occasional case, however, optimal assessment of an abnormality is aided by immunohistochemical stains.[85–87] Immunohistochemistry generally is most helpful either to assess trophoblastic tissue or to evaluate a neoplasm. Despite the large number of antibodies available, only a few are useful adjuncts for the diagnosis of most endometrial lesions. The applications of immunohistochemistry for specific diagnoses also are discussed in greater detail in the relevant chapters. The following is a brief summary of instances in which immunohistochemistry can assist in the diagnosis.

For trophoblastic tissue, one of the most useful immunostains is keratin. Because trophoblastic cells are epithelial, any type of trophoblast (cytotrophoblast, intermediate trophoblast, or syncytiotrophoblast) is immunoreactive to keratin unless fixation and preservation have masked the presence of the filaments. Consequently, a keratin stain can be very useful for demonstrating trophoblastic cells, especially intermediate trophoblast, in specimens in which chorionic villi and trophoblastic cells are not clearly evident. An example would be identification of trophoblast in assessing the possible presence of an ectopic pregnancy.[88–92] In these cases the infiltrate of intermediate trophoblast at the placental implantation site can be very difficult to distinguish from decidua (see Chapter 3). In addition to keratin, the placental hormones human chorionic gonadotropin-β (hCG-β), human placental lactogen (hPL), and Mel-CAM (CD 146) are produced by syncytiotrophoblast and intermediate trophoblast. Immunostains for these proteins, especially hPL and Mel-CAM, which are present in intermediate trophoblast at the placental implantation site, can be helpful in ruling out an ectopic pregnancy.[88;89;91–96]

Demonstration of hCG, hPL, Mel-CAM, and inhibin-α also is useful in establishing the diagnosis of choriocarcinoma, and placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor when routine H&E sections fail to clearly demonstrate the diagnostic histologic features of these neoplasms (see Chapter 4).[93;95;97–99] Inhibin-α also is a helpful immunohistochemical marker for the epithelioid trophoblastic tumor.[99;100] Differential staining of trophoblastic and proliferation markers also helps distinguish between the different types of trophoblastic tumors. Choriocarcinoma is more strongly reactive with hCG while the PSTT generally shows more staining for hPL. The Ki-67 proliferation index is also much higher in choriocarcinoma (>50%) as compared to PSTT (15% to 20%).[101] The

epithelioid trophoblastic tumor stains best with inhibin-α and p63 but shows only limited staining for hCG, hPL, and Mel-CAM.[95;100;100a] The Ki-67 proliferation index of this tumor is approximately 20%.[95] The proliferation marker Ki-67 also can be useful in distinguishing an exaggerated placental site from the placental site trophoblastic tumor (PSTT). The exaggerated placental site has no mitotic activity and a Ki-67 index near zero while in PSTT the proliferation index is 14% ± 6.9%.[101]

Immunohistochemistry can also be helpful in diagnosis of the placental site nodule. The intermediate cells of this lesion are reactive for keratin and EMA as well as placental alkaline phosphatase (PLAP), inhibin-α, and p63. The Ki-67 proliferation index is less than 10%. The placental site nodule is only focally reactive for hPL and Mel-CAM while the PSTT stains more diffusely for these antigens.[99] Also, the PSTT is not reactive for PLAP.

In early pregnancy the endometrial glands are immunoreactive for S-100 protein, and this staining disappears after the 12th week of gestation.[102;103] Normal proliferative and secretory endometrium and hyperplastic and neoplastic glands do not stain for S-100 protein. No antibodies assist in distinguishing atypical hyperplasia from well-differentiated adenocarcinoma.

Endometrial intraepithelial carcinoma (EIC) (see Chapter 9) and serous and clear cell carcinomas of the endometrium (see Chapter 10) show diffuse and strong reactivity for Ki-67, which demonstrates the high proliferative index of these lesions.[86;104–106] EIC and serous and clear cell carcinoma also are often strongly immunoreactive for p53, while endometrioid-type endometrial carcinomas are generally not.[86;105] Estrogen receptors also are usually absent in serous and clear cell carcinoma, in contrast to their presence in low-grade endometrioid carcinomas.[86;105;107]

In the evaluation of neoplasia, immunohistochemical stains may assist in the differential diagnosis of endometrial and endocervical primary adenocarcinoma. Endometrial carcinoma generally is immunoreactive for estrogen and progesterone receptor protein whereas endocervical carcinoma is not.[108–111] In addition, detection of human papilloma virus (HPV) by in situ hybridization is seen in endocervical but not endometrial carcinomas.[108] Also, virtually all of the usual types of endocervical carcinomas react with p16 whereas most of the typical endometrioid carcinomas arising in the uterine corpus do not.[112;113] Other immunostains also may be helpful but less specific in this distinction of primary site. For instance, vimentin frequently stains endometrial carcinomas while cervical adenocarcinomas are negative.[114;85;115;109;110;116] Conversely, carcinoembryonic antigen (CEA) often is present in endocervical carcinomas but is less common in endometrial primary tumors[110;115–118] (see Chapter 10). However, neither vimentin nor CEA is a completely specific marker for primary site.

Keratin immunostains also can help to determine whether a solid proliferation of cells represents an epithelial tumor or a lesion of mesenchymal or lymphoid cells. If the lesion represents a malignant mixed mesodermal tumor (MMMT) (carcinosarcoma), keratin staining also is useful for highlighting the biphasic nature of the tumor, with the keratin-positive epithelial component standing out against the background of mostly nonreactive sarcomatous cells (see Chapter 11).[119–124] Epithelial membrane antigen (EMA) also stains epithelial components. The sarcomatous spindle cell component may stain focally with keratin and EMA, but this staining is limited and less intense than the reactivity of the clearly carcinomatous component.[119–125]

In assessing a possible MMMT, other markers can be useful for establishing the presence of sarcomatous elements, although the subtype of sarcoma has no influence on the prognosis of the lesion. The sarcomatous component typically is reactive for vimentin and actin, and if the sarcomatous component includes leiomyosarcoma or rhabdomyosarcoma, muscle-specific actin and desmin reactivity also is found.[119;120;123–125] Myoglobin and myogenin are more specific stains for rhabdomyoblasts.[122;123] Occasionally other stains are useful. A tumor with glial differentiation will stain for S-100 protein or glial fibrillary acidic protein. Cartilaginous tissue is immunoreactive

for S-100 protein. Although immunohistochemical stains are useful adjuncts for tumor diagnosis, correlation of histologic features with immunoreactivity is essential for proper classification of cell types.

Endometrial stromal tumors are immunoreactive for CD10, actin, and, rarely, desmin.[126–128] Smooth muscle tumors are more diffusely reactive for desmin and also are positive for h-caldesmon.[129;130] Both stromal and smooth muscle tumors also may show immunoreactivity for keratin, although the staining usually is focal, so positive staining for keratin needs to be carefully assessed, especially for the number and intensity of positive cells. In contrast to keratin, EMA is much more specific as an epithelial marker in our experience. It is not present in stromal or smooth muscle tumors.

Other applications of immunohistochemistry are relatively infrequent. On occasion the endometrium will contain metastatic tumor from an unknown primary site, and immunohistochemical evaluation can help determine the type of tumor present.[131] An immunostain for S-100 protein can help identify metastatic melanoma. Metastatic carcinoma from the gastrointestinal tract typically is immunoreactive for cytokeratin 20 and CEA, whereas primary endometrial cancer usually is not. Metastatic breast carcinoma often shows immunostaining for gross cystic disease fluid protein-15.[131] Lymphoma and leukemia can be characterized using a number of lymphoid markers.[132] Antibodies for herpesvirus and cytomegalovirus can help establish the presence of these viral infections.

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