Radiological Reasoning: Algorithmic Workup of Abnormal Vaginal Bleeding with Endovaginal Sonography and Sonohysterography

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OBJECTIVE

The workup of endometrial abnormalities can be a confusing task for radiologists because one must take into account the patient’s clinical history, imaging findings, and a wide array of diagnostic options. We present two cases, one of a premenopausal woman presenting with vaginal bleeding and another of a postmenopausal woman taking tamoxifen who has abnormal findings on endovaginal sonography. The evaluations of these patients serve to illustrate the diagnostic algorithm for identification of endometrial pathology.

CONCLUSION

Imaging plays a central role in the algorithm for detection of endometrial disorders in women with abnormal vaginal bleeding. Endovaginal sonography is used to identify mural abnormalities such as fibroids and adenomyosis and to screen for thickened endometria that require nonfocal biopsy for the diagnosis of cancer or hyperplasia. Sonohysterography serves as a triage tool to detect focal abnormalities of the endometrial cavity, such as endometrial polyps or subendometrial fibroids, thereby identifying those women who require more invasive workup with hysteroscopy.

Case History, Patient 1

A 32-year-old nulligravida woman with no significant medical history presents complaining of significant intermenstrual bleeding. Her pelvic examination is normal. Her uterus is small, mobile, and nontender. No adnexal masses or tenderness is noted. Her $\beta$-HCG is negative. A trial of hormonal therapy has not been successful. Pelvic sonography is performed.

Sonography

On endovaginal sonography (Fig. 1A), a 15-mm homogeneously echogenic endometrial echo complex is noted, which is within normal limits. A “hyperechoic line sign” \cite{1}, a line circumscribing the central endometrial complex, is seen, suggesting a focal intracavitary abnormality such as a polyp. Sonohysterography is recommended.

Expert Discussion (Dr. Lee)

In premenopausal women with bleeding, benign causes—for example, endometrial polyps and fibroids—constitute most of the abnormalities detected on imaging. Endovaginal sonography is a good first step to screen for mural as well as endometrial abnormalities. However, the diagnostic performance of endovaginal sonography for detecting endometrial pathology in premenopausal women is moderate, with sensitivity and specificity of 67% and 75%, respectively, using an endometrial thickness cutoff of $>16\text{ mm}$ \cite{2}.

If endovaginal sonography indicates endometrial abnormality, nonfocal endometrial biopsy should be performed to exclude cancer or hyperplasia—that is, diffuse endometrial pathology. Even if cancer is an unlikely possibility, it should not be missed because it is the one cause of abnormal vaginal bleeding that is life-threatening. A nonfocal biopsy is a relatively noninvasive, inexpensive office procedure to evaluate for endometrial cancer. Once biopsy is negative for cancer or hyperplasia (a premalignant lesion), workup should continue to evaluate for the focal benign cause of bleeding.

This patient shows a homogeneous endometrial echo complex that has a thickness that is within normal limits. Thus, the vaginal bleeding is unlikely secondary to a diffuse endometrial process, such as endometrial carcinoma, and a nonfocal biopsy is not indicated. The next step is to evaluate for focal causes for bleeding, which are best detected by sonohysterography.

Sonohysterography

The endometrium measures 1 mm anteriorly and 1 mm posteriorly. In the endometrial canal is a $2.5 \times 1.7\text{ cm}$ homogeneously hyperechoic lesion, with attachment at the 6-o’clock position on coronal images, and showing a central stalk on color Doppler imaging (Fig. 1B).

Expert Discussion (Dr. Lee)

The differential diagnosis of focal endometrial abnormality seen on sonohysterography includes polyp, subendometrial fibroid, focal cancer, and hyperplasia. Although cancer

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and hyperplasia are a consideration, they would more typically show a broad base of attachment and appear diffuse.

Endometrial polyps are localized hyperplastic overgrowths of endometrial glands and stroma around a vascular core that form a sessile or pedunculated projection from the surface of the endometrium. Single or multiple polyps can occur ranging from a few millimeters to several centimeters in size. On sonohysterography, polyps appear as echogenic, smooth, intracavitary masses outlined by fluid [3, 4]. Color Doppler images may show a single feeding artery at the base of attachment, as seen in this patient, a finding frequently seen with polyps [5].

The sonographic appearance of polyps can be variable. Cystic spaces corresponding to dilated glands filled with proteinaceous fluid may also be seen. The polyp may show a narrow stalk but can occasionally appear broad-based or sessile. The point of attachment does not disrupt the endometrial lining. At times polyps show heterogeneous echotexture, indicating hemorrhage, infarction, or inflammation [6]. Foci of hyperplasia or malignant degeneration cannot be excluded with imaging. Thus, even though most polyps are benign, those that cause bleeding are resected for histologic evaluation to exclude malignancy.

Another cause of focal endometrial abnormality on sonohysterography is subendometrial fibroids. Subendometrial fibroids are typically hypoechoic, well-defined solid masses, with either a narrow or a broad base of attachment. Most important, they show an overlying layer of echogenic endometrium. They often distort the interface between the endometrium and myometrium and show acoustic attenuation. Subendometrial fibroids are often larger than polyps and may show multiple feeding vessels [7]. The key to differentiating the two entities is to ascertain the location of the endometrial lining with regard to the lesion. In this patient, a fibroid is not likely because the endometrium subtends the focal lesion.

Endometrial hyperplasia is caused by unopposed estrogen stimulation. Risk factors include endogenous or exogenous exposure to estrogen, use of tamoxifen, nulliparity, obesity, hypertension, and diabetes. On sonohysterography, endometrial hyperplasia usually appears as a diffuse thickening of the endometrial echo complex. Although hyperplasia typically presents as a diffuse endometrial abnormality, focality is occasionally seen.

Endometrial cancer has the same risk factors and overlapping imaging appearance as hyperplasia. The most common appearance is nonspecific thickening. On sonohysterography, the diagnosis should be suspected when a single layer is thicker than 8 mm, irregular, broad-based, poorly marginated, or when the endometrial–myometrial interface is disrupted [5]. On occasion, early cases of endometrial cancer can be polypoid.

In summary, the imaging features of the endometrial abnormality in this premenopausal patient are most in keeping with an endometrial polyp. However, fibroids, focal endometrial hyperplasia, or carcinoma can mimic a sessile polyp, and foci of atypical hyperplasia are sometimes found in polyps. The next step in the workup of this patient is histologic resection of the focal endometrial lesion under hysteroscopic guidance.

Hysteroscopy

Visualization of the endometrial cavity reveals it to be completely normal in size, shape, and position. A 2.5-cm

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**Fig. 1**—32-year-old premenopausal woman with abnormal vaginal bleeding. 
**A.** Coronal endovaginal sonogram shows endometrial echo complex measuring 15 mm, which is within normal limits. Note hyperechoic line (arrows) circumscribing thickened endometrium, suggesting focal endometrial abnormality. 
**B.** Color Doppler sonohysterogram shows hyperechoic intracavitary lesion (solid arrows) and stalk of increased vascular flow (open arrow).
endometrial polyp is attached to a narrow stalk on the posterior wall of the uterus.

Pathology

Three fragments of tan and pink glistening polypoid soft tissue were obtained, measuring in aggregate $2.7 \times 2.2 \times 0.9$ cm. They were negative for malignancy.

Case History, Patient 2

A 68-year-old woman with a history of stage T1b, N0 invasive ductal carcinoma of the right breast has been taking tamoxifen for 2 years. The patient is G5, P6, underwent menopause at age 50, and has undergone 12 years of progestone-only hormone replacement therapy. She experienced an episode of pelvic pain but denies vaginal bleeding. Physical examination of the abdomen and pelvis is normal. She is referred for pelvic sonography.

Sonography

The endometrial echo complex shows apparent thickening (Fig. 2A) measuring 16 mm. Multiple cystic structures are noted in the endometrial echo complex that could be either subendometrial or endometrial. Differential considerations include an endometrial process, such as a polyp or hyperplasia, or a subendometrial process, such as cystic subendometrial atrophy. Because the subsequent nonfocal endometrial biopsy reveals only atrophy, sonohysterography is recommended to differentiate.

Expert Discussion (Dr. Lee)

The use of tamoxifen as an adjunctive treatment for breast cancer has resulted in an increased prevalence of endometrial polyps, hyperplasia, and carcinoma. This drug is an estrogen antagonist in the breast but has a weak estrogenic effect in the uterus [8, 9]. Because of the resulting

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**Fig. 2**—68-year-old postmenopausal woman receiving tamoxifen.
A, Transvaginal sonography shows multiple cystic foci (arrows) that may be either subendometrial or endometrial. Endometrial echo complex appears thick, measuring 16 mm.
B, Sonohysterography shows two polypoid lesions (arrows) in endometrial canal.
C, Second sonohysterography image shows cystic changes (arrows) subtending echogenic endometrial lining, a finding commonly seen with tamoxifen use.
Sonohysterography and Sonohysterography of Vaginal Bleeding

increased risk for endometrial malignancy, endometrial abnormalities detected on sonography should be worked up aggressively in this group of patients.

On screening endovaginal sonography, postmenopausal women taking tamoxifen show endometria that are frequently thicker than those of control subjects [9], and the thickness seems to correlate with duration of tamoxifen treatment [10]. Most women with thickened endometria are asymptomatic. Some investigators have proposed using 5–8 mm as a cutoff for diagnosing endometrial abnormalities on endovaginal sonography in asymptomatic postmenopausal women receiving tamoxifen [11–13].

The cystic changes seen in this patient may be associated with an endometrial polyp, subendometrial cystic atrophy related to tamoxifen, or adenomyosis. Thus, in patients who have had long-term exposure to tamoxifen, it is often difficult to delineate an endometrial from a subendometrial process on endovaginal sonography. Furthermore, abnormalities such as endometrial polyp or carcinoma coexist, limiting the use of endovaginal sonography in the diagnosis of specific abnormalities in this patient population [14].

Because in this patient endovaginal sonography indicates apparent thickening of the endometrium, the first step in management is a nonfocal endometrial biopsy to evaluate for cancer or hyperplasia. When this proves negative, the next step is to proceed with a workup for a focal abnormality. Sonohysterography has been shown to perform more accurately than endovaginal sonography in the detection of focal endometrial abnormalities [10, 14] and to obviate surgery in some cases [15].

Sonohysterography

An 8-mm polypoid lesion and a 6-mm polypoid lesion arising from the posterior endometrium (Fig. 2B) are noted. The cystic changes that appeared as apparent endometrial thickening on endovaginal sonography are shown on sonohysterography to be subendometrial and consistent with the patient’s history of chronic tamoxifen exposure (Fig. 2C).

Expert Discussion (Dr. Lee)

Cystic spaces in the uterine myometrium are a frequent finding in patients receiving tamoxifen. Some investigators believe that the cystic spaces reside in the inner myometrium and are associated with an increased prevalence of adenomyosis or adenomyosis-like changes [16]. Others hypothesize that these changes are due to atrophy [17]. Regardless of the cause, the cystic changes may simulate endometrial thickening on endovaginal sonography. Sonohysterography distinguishes endometrial from subendometrial abnormalities. Thus, in women with chronic tamoxifen exposure and abnormalities on endovaginal sonography, sonohysterography can be used to triage those requiring hysteroscopic resection of focal endometrial abnormalities from those who have no endometrial abnormalities.

The differential diagnosis for polypoid lesions arising from the posterior wall is an endometrial polyp and, less likely, focal hyperplasia or cancer. As with the previous patient, because imaging cannot exclude endometrial malignancy, the next step is histologic evaluation.

Hysteroscopy

Two foci of posterior endometrial thickening are seen, consistent with polyps. Biopsy of the focal lesions as well as the nonthickened surrounding endometrium is performed.

Pathology

Biopsy of the focal lesions reveals marked glandular atypia consistent with a polyp or reparative change. Atrophy is noted in the biopsy of the surrounding nonthickened endometrium.

Commentary

Figure 3 presents an algorithm for evaluating abnormal vaginal bleeding in both pre- and postmenopausal women. The major diagnostic tools include endovaginal sonography, nonfocal endometrial biopsy, sonohysterography, and hysteroscopy. Endometrial lesions are classified as nonfocal (cancer and hyperplasia) or focal (polyps and submucosal fibroids). Nonfocal abnormalities are considered malignant or premalignant, whereas most focal lesions are benign. Endometrial cancer is a relatively rare cause of abnormal bleeding, estimated to account for 10% of postmenopausal bleeding, and probably even an order of magnitude less of premenopausal abnormal bleeding [18]. However, cancer is the only cause of vaginal bleeding from an endometrial source that is potentially lethal; hence, the primary goal in the workup of abnormal bleeding is to exclude malignancy. Only after cancer has been deemed unlikely, either by lack of patient risk factors, normal endometrial thickness on endovaginal sonography, or negative nonfocal endometrial biopsy, should a focal, more likely benign cause be sought to explain the bleeding. The tools for identifying focal abnormalities are sonohysterography and hysteroscopy.

Sonohysterography and hysteroscopy show similar performance characteristics with regard to sensitivity (95–96%) and specificity (88–90%) for detecting and characterizing focal endometrial abnormalities [19, 20]. Hysteroscopy has the advantage of yielding a tissue diagnosis, with the drawback of greater patient discomfort, expense, and, rarely, the major complication of uterine perforation. Sonohysterography is less invasive, less expensive, well tolerated, and without major complications. In addition, sonohysterography provides a road map for hysteroscopic resection of intracavitary lesions and reduces the number of negative hysteroscopies. Nonetheless, it is an added step in the workup, and its role in the diagnostic algorithm of endometrial abnormality remains to be investigated [21, 22]. Among the subset of postmenopausal women taking tamoxifen, however, in whom endovaginal sonography results are often
nonspecific, sonohysterography is useful for distinguishing endometrial from subendometrial abnormalities and thereby guiding diagnostic workup [8].

In most premenopausal women, endometrial cancer is rare. The most common cause of bleeding is hormonal or mural lesions (e.g., fibroids or adenomyosis). Thus, the first step in managing a premenopausal woman who is not at high risk for endometrial cancer—high-risk factors are age > 35 years, morbid obesity, chronic hypertension, chronic diabetes, and chronic tamoxifen exposure—is a trial of hormonal therapy. Sonography is usually performed to evaluate for mural lesions. Endovaginal sonography is less useful for the detection of endometrial abnormalities because normal endometrial thickness varies widely in the premenopausal population. In general, a thickness of greater than 16 mm in a symptomatic patient is considered abnormal, but with suboptimal sensitivity (67%) and specificity (75%) [2]. If hormonal therapy fails, if woman is at high risk for endometrial cancer, or if endovaginal sonography shows an endometrial abnormality, endometrial biopsy is performed to evaluate for cancer or hyperplasia. If the nonfocal biopsy is negative for cancer, then workup proceeds with sonohysterography or hysteroscopy to evaluate for focal lesions.

In postmenopausal women, the most likely causes of abnormal bleeding are benign, such as fibroids, endometrial polyps, or atrophy. However, abnormal bleeding in postmenopausal women carries a much higher likelihood of harboring malignancy than in premenopausal women. Thus, in postmenopausal women, endovaginal sonography is a well-tolerated, inexpensive way to initially screen for endometrial cancer. With an endometrial thickness cutoff of > 5 mm considered abnormal, endovaginal sonography is the most sensitive technique for detecting endometrial cancer (96% sensitivity), better than nonfocal biopsy (87% sensitivity), sonohysterography (89% sensitivity), or hysteroscopy (86% sensitivity) [18, 23]. For symptomatic postmenopausal women, a thickness of < 5 mm indicates that bleeding is likely secondary to endometrial atrophy [24]. The algorithm for working up postmenopausal women undergoing hormone replacement therapy follows similar reasoning, using endovaginal sonography as the first-line screening technique for endometrial cancer. A thickness of 8 mm is considered the upper limit of normal if the patient is asymptomatic [25]. However, if the patient reports postmenopausal bleeding, a thickness cutoff of > 5 mm is used with a sensitivity for cancer similar to that in women who are not receiving hormone replacement therapy [26].

For women taking tamoxifen, endovaginal sonography is of limited usefulness in evaluating the endometrium because tamoxifen-induced subendometrial changes can mimic a thickened endometrial echo complex. Thus, what is considered normal endometrial thickness in an asymptomatic woman is controversial in this patient population. However, because of the higher risk of malignancy among these patients, abnormal vaginal bleeding requires further evaluation, starting with nonfocal biopsy to exclude malignancy.

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**Fig. 3**—Algorithm for evaluating women with abnormal vaginal bleeding. In asymptomatic postmenopausal women, endometrial thickness of > 6 mm (or patients not undergoing hormone replacement therapy) or > 8 mm (for those receiving hormone replacement therapy) is considered abnormal and should trigger a similar workup for endometrial abnormalities [24]. Threshold for workup of asymptomatic women taking tamoxifen is controversial, with endometrial thickness cutoffs of 5–8 mm having been proposed. D&C = dilatation and curettage.
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nancy, regardless of endometrial thickness [27]. Sonohysterography plays an important role as an adjunct to endovaginal sonography by delineating endometrial and subendometrial disorders and selecting patients requiring hysteroscopy.

The role of MRI in the workup of abnormal vaginal bleeding is less clear. MRI is indicated if bleeding is attributed to leiomyomas and myomectomy is contemplated, or if sonography is indeterminate in differentiating adenomyosis from leiomyomas [28]. MRI may also be appropriate in patients who cannot undergo endovaginal sonography or in those with an equivocal or abnormal endovaginal sonography finding who cannot undergo sonohysterography.

Conclusion
Histology constitutes the definitive diagnosis in all women with abnormal vaginal bleeding that is unresponsive to medical or hormonal therapy. However, imaging plays a key role in screening and diagnostic triage. Endovaginal sonography is used to identify mural abnormalities, such as fibroids and adenomyosis, and to screen for thickened endometria which require nonfocal biopsy to detect cancer or hyperplasia. Sonohysterography is a powerful tool for evaluating the endometrial cavity for focal abnormalities such as endometrial polyps or submucosal fibroids. It thereby identifies those women who require more invasive workup with hysteroscopy and provides a roadmap for hysteroscopic resection of intracavitary lesions.

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