

# Investigation of Abnormal Uterine Bleeding in Peri- and Postmenopausal Women

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The ovarian life cycle spans 4 decades, with most women having approximately 450–500 menstrual cycles during a lifetime. Irregularity in menstrual cycles is frequent during the perimenopausal years, but is often only a nuisance, with malignancy rarely the cause. Such bleeding becomes greater cause for concern when it occurs during the postmenopausal years.

Each year there are more than 2.5 million visits to gynecologists for the evaluation of abnormal uterine bleeding. Physicians must maintain a low threshold for endometrial assessment in postmenopausal women who present with abnormal bleeding. Accurately determining the etiology of the bleeding permits appropriate treatment, minimizes unnecessary delays in therapy and prevents needless worry in patients. Fortunately, medical therapy is effective and appropriate for the majority of patients; only when response to medical therapy is less than satisfactory should organic disease, intrauterine pathology and endocrine abnormalities be ruled out.

This article will address the salient issues and office-based options available for the evaluation of abnormal uterine bleeding in this group of women.

## Abnormal Pre- and Perimenopausal Bleeding

Abnormal uterine bleeding in reproductive-age women is common, leading to one-third of outpatient visits by this population. The most frequent culprits in this age group include anovulation, polycystic ovary syndrome, structural abnormalities (polyps, fibroids), endometrial hyperplasia, cancer, foreign bodies, pregnancy-

related complications, disorders of hemostasis, trauma and infection.

Menstrual aberrations occur at the extremes of the reproductive life cycle. Within the first 1–5 years after the onset of menstruation, and also beginning by the late 30s and 40s, periodic or persistent menstrual dysfunction is typical. Approximately 50% of women by age 45.5 years, 75% by age 47.8 years and 95% by

age 50.8 years will experience menstrual abnormalities.<sup>1</sup>

Anovulation is the most common culprit in menstrual dysfunction during the transition years. Rarely should surgical intervention be the first step in the evaluation of perimenopausal abnormal bleeding. Rather, the gynecologist should evaluate the most likely etiology via medical history and pelvic evaluation and, in the absence of any suggestion of pathology, should first aggressively treat medically with hormonal contraceptives, progesterone therapy or with a medicated intrauterine system (Mirena intrauterine device).

In addition to anovulatory cycles, reproductive-age patients may also have intrauterine structural abnormalities that contribute to abnormal bleeding. The most conservative approaches to management of abnormal bleeding in such cases include “watchful waiting”, medical therapy and, when such therapy fails or the patient is markedly anemic, visualization or imaging of the endometrial cavity. Treatment initiatives include methods to regulate menstrual cycles, minimize blood loss and prevent complications of chronic unopposed estrogen stimulation.

Seltzer et al<sup>2</sup> retrospectively followed 500 perimenopausal women and systematically noted that the classic categories of bleeding typical of the

perimenopause included hypomenorrhea (70%); menorrhagia, metrorrhagia and/or hypermenorrhea (18%); and sudden cessation of menses (12%). Using multiple hormonal analyses, Landgren et al<sup>3</sup> evaluated 13 women longitudinally, between 4 and 9 years before menopause. They noted increased frequency of anovulatory cycles characterized by elevated follicle-stimulating hormone (FSH) concentrations 30 cycles before final menstruation occurred. Women with hormonal evidence of ovulatory cycles did not have FSH levels that rose consistently.

### Evaluation (Perimenopausal Bleeding)

Transvaginal ultrasound (TVUS) has been the gold standard of imaging in the postmenopausal patient; however, in the reproductive-age patient TVUS is less accurate in the diagnosis of focal endometrial pathology.<sup>4</sup> The sensitivity of TVUS for detecting all intracavitary lesions has ranged from 48% to 96% and the specificity has ranged from 68% to 95%.<sup>5,6</sup> A recent study by Breitkopf and colleagues<sup>7</sup> highlights the limitations of TVUS alone in reproductive-age patients and, when possible, strongly advocates the addition of saline infusion to improve detection of intracavitary lesions and myometrial abnormalities in this age group. When saline infusion sonography (SIS) is not available, in-office hysteroscopy can be used to quickly and comfortably evaluate the endometrium. In this study the investigators evaluated 206 premenopausal women who had normal endometrial echoes. They determined that one in six lesions was missed when TVUS was used alone. Specifically, of 80 subjects with an endometrial echo of  $\leq 5$  mm, 11 had endometrial polyps and 5 had submucosal fibroids that

were detected only with SIS. The investigators found that SIS provided more accurate information regarding the presence of intracavitary pathology.

### Postmenopausal Bleeding

The average age at which women experience menopause has remained steady, occurring in 80% of women by age 51, and 95% of women by age



Numerically, the highest rate of PMB occurs within the 5 years after spontaneous amenorrhea, and gradually declines thereafter.

In almost all studies to date, SIS has been shown to be more sensitive and reliable than TVUS in detecting endometrial polyps and submucosal fibroids. When used without concomitant endometrial biopsy, SIS is less sensitive in diagnosing endometrial hyperplasia in the perimenopausal population.<sup>8</sup>

In-office hysteroscopy performed for a more comprehensive evaluation of the endometrium is a reasonable option when a patient continues to have abnormal uterine bleeding despite medical therapy, and has undergone only TVUS (without SIS). The Breitkopf study suggests that an endometrial echo of  $\leq 5$  mm cannot exclude benign endometrial pathology in premenopausal patients.

55, with virtually all women experiencing cessation of menses by age 58. Postmenopausal bleeding (PMB) is defined as any bleeding that occurs 12 months after the last menstrual period. After years of amenorrhea, the onset of any vaginal bleeding is cause for concern on the part of both clinician and patient. Even small amounts of bleeding should elicit prompt and thorough evaluation. Additionally, acyclical vaginal bleeding in postmenopausal women receiving hormone therapy (HT) warrants evaluation.

Numerically, the highest rate of PMB occurs within the 5 years after spontaneous amenorrhea, and gradually declines thereafter. In a prospective, observational, population-based study,

297 postmenopausal women completed 1 year of daily recording of bleeding.<sup>9</sup> PMB occurred in 409 per 1,000 person-years in the first year immediately after menopause. When more than 3 years elapsed, the rate plummeted to 42 per 1,000 person-years.

**Endometrial cancer.** Endometrial cancer is the most common genital female malignancy,<sup>10</sup> accounting for nearly half of all new cases of genital cancer. The probability of endometrial cancer in women presenting with PMB is approximately 5–15%,<sup>10</sup> and the lifetime risk of being diagnosed with the disease is 2.7%.<sup>10</sup> The median age at diagnosis is 63 years. Risk factors include obesity, use of unopposed estrogen therapy, prolonged tamoxifen use, anovulation, polycystic ovary syndrome, estrogen-secreting tumors, nulliparity, late menopause and history of complex endometrial hyperplasia with atypia.

Although the total mortality rate for women with endometrial cancer has decreased since the 1980s, this is not an indolent disease. Stage for stage, endometrial cancer is just as lethal as ovarian cancer. But because of a usually excellent prognosis, endometrial cancer is often referred to as the “curable cancer” because of early detection and prompt surgical intervention. Unlike women with ovarian cancer, most patients with endometrial cancer are symptomatic and present with PMB or a lengthy bout of perimenopausal bleeding. Indeed, the presence of symptoms (bleeding, pelvic cramping or unexplained chronic vaginal discharge) is the tangible hallmark of endometrial cancer, which should prompt early investigation, identification and initiation of treatment, assuring a better prognosis. Overall 5-year survival is 86%; when the disease is confined within the uterus 5-year survival rates peak at 97%.<sup>11</sup> Although endometrial cancer is 40%

more common in white women, black women are twice as likely to die from the disease; black women tend to be diagnosed later, have a more advanced stage of cancer upon diagnosis, and a more lethal histologic subtype (serous tumors) than do white women.

Clinicians must carefully evaluate any abnormal bleeding in older women, since 95% of endometrial cancers occur in women age 40 and older, and because endometrial hyperplasia, the precursor state, may precede the diagnosis.<sup>11</sup>

**Ovarian, cervical and fallopian tube cancers.** Gredmark and colleagues report that, together, ovarian and cervical cancer occur in 3% of women with PMB.<sup>12</sup> Fallopian tube carcinoma, a true rarity, must also be considered when persistent vaginal bleeding occurs despite a negative evaluation of the endometrium. These statistics are important to remember, especially when a patient continues to bleed after a negative evaluation of the uterine cavity. The adnexa and the bladder should be evaluated (urine cytology and bladder imaging) when endometrial evaluation is unremarkable in the presence of genital bleeding.

### Evaluation of Postmenopausal Bleeding

The work-up of patients with PMB should always be thorough. Clinical evaluation of PMB can be accomplished with a number of diagnostic methods and tools.

**Endometrial biopsy and TVUS.** Traditionally, endometrial biopsy has been considered the gold standard for the evaluation of PMB, with both clinician and patient reassured by a normal biopsy result. The challenge, however, is the two-thirds of patients with PMB who have an endometrial biopsy that demonstrates endometrial atrophy or “tissue insufficient for diagnosis.” In these cases the clinician is

usually concerned about having missed a focal lesion. Karlsson et al reviewed 1,168 cases of PMB evaluated with TVUS followed by dilation and curettage,<sup>13</sup> including 351 women (ages 41 to 91 years) taking HT. They found that PMB was due to the following causes: endometrial atrophy (>59% of cases); polyps (12%); endometrial cancer (10%); endometrial hyperplasia (9.8%); hormonal effect (7%); hydrometra, pyometra and hematometra (2%); and cervical cancer (<1%).

TVUS endometrial measurement (endometrial echo/endometrial stripe) is helpful in categorizing patients into a low- versus high-risk group. The exact cutoff measurement chosen is a function of the sensitivity and specificity sought. Most clinicians use a cutoff of 5 mm to define a low-risk patient group, whose combined risk for cancer and atypical hyperplasia ranges from 2% to 3%. The initial goal of TVUS was not to replace endometrial biopsy, but to decrease the number of endometrial biopsies needed.<sup>14</sup> Ultrasonographers painstakingly sought to find the specific endometrial echo length for which the likelihood of missing endometrial cancer would be exceedingly low.<sup>15</sup>

Criteria for stratification into low-risk groups include age less than 70 years, multiparous status, bleeding that occurs within 1 year of menopause and absence of diabetes. In contrast, patients with an endometrial echo >5 mm have an increased risk of endometrial cancer and atypical hyperplasia approaching 5% or more. Patients with all four risk factors—diabetes, nulliparity, age >70 years and bleeding that occurs more than 1 year after menopause—have a relative risk of 1.8 compared with a low-risk population.<sup>16</sup> However, many evaluations of the usefulness of the endometrial measurement have included asymptomatic patients. It may therefore be

that patients presenting with bleeding have a higher detection rate than asymptomatic patients.

**SIS and hysteroscopy.** TVUS and, when available, SIS should be considered in the work-up. When the patient's bleeding persists despite a negative biopsy or normal TVUS, continue to evaluate with additional technology. If only TVUS (Figures 1 and 2) and endometrial biopsy were initially utilized, direct inspection of the endometrium with in-office hysteroscopy or SIS should be considered if bleeding recurs. The interface created by fluid during SIS effectively delineates intraluminal defects (Figures 3 and 4). Likewise, direct visualization of the endometrium with hysteroscopy detects intracavitary pathology.<sup>17</sup> Several authors have found that when women were followed after a negative initial endometrial biopsy, 20% with persistent or episodic vaginal bleeding were ultimately diagnosed with either complex atypical hyperplasia or cancer.<sup>18</sup> Vigilance and the use of additional technology are important to minimize the chance of missing intracavitary pathology.

**Pelvic examination.** Pelvic examination should include thorough inspection of the vagina, vaginal fornices, vulva, vaginal vault and urethra for lesions. Vaginal atrophy is a frequent cause of abnormal bleeding; thin, friable tissue that bleeds easily with intercourse or spontaneously is common with each advancing decade. Any vulvar lesion with chronic excoriation should be biopsied liberally. Vaginoscopy can be used to detect subtle vaginal ulceration, foreign bodies and lesions. When vaginal atrophy is noted, an excellent response to oral or topical estrogen therapy is the norm.

**Cervical cytology.** While not a screening tool for endometrial cancer, the Pap test must be included in

the PMB work-up to exclude cervical or endocervical causes of bleeding. A liquid-based Pap smear is warranted for all women with new-onset PMB, even when the patient has undergone cervical cytology within the past 1 to 3 years. Even though newer cervical cytology guidelines propose less frequent Pap tests after age 60, there is a bimodal distribution of cervical cancer, as well as its indolent endocervical adenocarcinoma counterpart. A smear with atypical glandular cells is associated with a premalignant or

malignant lesion of the endocervix or endometrium in 10–40% of cases.<sup>19</sup> Therefore, all women over age 35 and younger women with unexplained bleeding and atypical glandular cells on the smear require further, more invasive testing.<sup>19</sup>

### Rethinking Evaluation Tools for Peri- and Postmenopausal Bleeding

Do we need to rethink the role of endometrial biopsy in the evaluation of patients with abnormal uterine bleed-



**Figure 1.** Transvaginal ultrasound, longitudinal view. Uterine measurement: 8.2 cm x 4.8 cm x 5.4 cm. The endometrial echo is ill-defined, with a hypoechoic mass.



**Figure 2.** Transvaginal ultrasound, coronal view. Uterine measurement: 8.2 cm x 4.8 cm x 5.4 cm. The endometrial echo is ill-defined, with a hypoechoic mass.

ing? Is endometrial biopsy, when used alone, an outdated modality in the algorithm of the evaluation of abnormal bleeding? Most studies demonstrate the inadequacy of blind endometrial sampling, including dilatation and curettage, in women with focal lesions.<sup>20</sup>

Increasingly, TVUS is proposed as the first-line, minimally invasive tool in the evaluation of PMB. In general, if TVUS is used alone, an endometrial stripe that is well delineated in its entirety, and is homogeneous, without fluid or irregularities will unlikely

harbor endometrial cancer when the endometrial echo is  $< 5$  mm and the patient has minimal risk factors.<sup>21</sup> The adnexa should also be imaged to rule out adnexal pathology. Using a threshold of  $< 5$  mm, an endometrial echo cutoff is the most cost-effective diagnostic strategy for detecting endometrial cancer.<sup>22</sup> However, an endometrial echo  $< 5$  mm can harbor other nonmalignant pathology that causes PMB, including endometrial atrophy, polyps, endometritis, submucosal fibroids, pyometra, and proliferative and

hyperplastic endometrium. For this reason, the clinician should not end the work-up in a patient who continues to have symptoms but has an endometrial echo  $< 5$  mm. When symptoms persist, or the amount of bleeding is profuse, then reevaluation with direct visualization via hysteroscopically directed biopsy or SIS is indicated. When a focal lesion is detected, hysteroscopic resection or directed biopsy is warranted.

Similarly, if a patient with PMB has a thickened endometrial echo, especially  $> 5$  mm, and has endometrial curettings obtained blindly or biopsy that is insufficient, additional evaluation with hysteroscopy or SIS is mandatory. Most of these patients will have a focally growing lesion, which can be hysteroscopically resected. Benign pathology, such as polyps and hyperplasia, causes bleeding. Less than 2% of polyps contain a malignancy or hyperplasia with/without atypia. But malignant changes within polyps can rarely be detected with ultrasound (including Doppler flow) or hysteroscopic visualization alone, and even small polyps  $< 2$  cm can be malignant.<sup>23</sup> A polypoid growth can actually be a focal area of hyperplasia, a malignancy or a mesenchymal tumor.<sup>24</sup> Obtaining histology is paramount when symptomatic abnormal bleeding is encountered.

A thorough review of the literature clearly delineates that when the endometrium is imaged entirely by TVUS, and is homogeneous and  $< 5$  mm, it will unlikely harbor endometrial cancer. However, TVUS alone rarely can determine the presence of focal lesions. It is the benign focal lesions that usually cause episodic and irregular bleeding. Facts to consider include the following:

- Findings from a meta-analysis of 35 studies involving 5,892 women and using an endometrial



**Figure 3.** SIS, longitudinal view, demonstrating a 2.3 cm x 1.9 cm x 2.7 cm intracavitary submucosal fibroid with a right lateral wall attachment site.



**Figure 4.** SIS, coronal view, demonstrating a 2.3 cm x 1.9 cm x 2.7 cm intracavitary submucosal fibroid with a right lateral wall attachment site.

thickness cutoff of 5 mm<sup>25</sup> revealed that this cutoff had > 92% sensitivity for detecting benign and malignant endometrial disease (polyps, atypical hyperplasia or cancer) and 96% sensitivity for detecting endometrial cancer. Therefore, a postmenopausal woman with a 10% pretest probability of endometrial cancer has a 1% probability of cancer if her TVUS has an endometrial echo < 5 mm.

- Tsuda et al<sup>26</sup> evaluated 600 postmenopausal women and used different endometrial echo cutoff values based on the number of years since menopause. If the patient was less than 5 years past the onset of menopause the endometrial echo was set at 4 mm; if more than 5 years menopausal the cutoff was 3 mm. TVUS demonstrated a 97.4% sensitivity, 75.7% specificity, a 23.8% positive predictive value and a 99.7% negative predictive value.
- Fleischer et al<sup>27</sup> used TVUS to evaluate 1,750 women without PMB for a selective estrogen-receptor modulator study. When the endometrial echo was < 5 mm the negative predictive value was 99.94% for excluding malignancy (1 cancer in 1,750 women) and 99.77% for complex hyperplasia (4 in 1,750 women).
- Gull et al<sup>28</sup> found that only 7 cancers in 1,361 women were found using a 4-mm cutoff.

*The 4mm cutoff.* The data are very solid for the use of TVUS in the evaluation of PMB. Literature review supports a conservative approach when the endometrial echo is < 4mm in a postmenopausal woman; the risk of missing an endometrial cancer is low. However, to rely upon TVUS the endometrial echo should be fully viewed,

and should appear homogeneous and without fluid. If the endometrial echo is indistinct, not visualized, irregular and has a heterogeneous appearance, then additional surveillance with SIS or hysteroscopy is mandatory. Addi-

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tionally, if bleeding recurs despite a normal TVUS, then a direct view of the endometrium is necessary. Despite a TVUS endometrial echo of < 4 mm in patients with persistent bleeding, either in-office hysteroscopy or SIS should be employed next to evaluate for subtle intracavitary lesions.

When the endometrial echo is > 4 mm, SIS or hysteroscopy should be performed. The distention of the endometrial cavity permits identification of focal lesions, polyps, fibroids, dyssynchronous endometrium, hyperplasia or cancer. If a focal lesion is identified, then a targeted endometrial biopsy (with full removal of the lesion) is the most sensitive method of determining the cause of the increased endometrial thickness. If a diffusely thickened endometrium is identified, a blind aspiration biopsy (with a pipelle or Vabra aspirate) provides a sensitive analysis. If endometrial biopsy yields insufficient tissue that is inadequate for evaluation, or if no endometrial tissue is obtained or stenosis is encountered, direct visualization of the endometrium should be performed and directed biopsies taken.

*Hysteroscopy.* Hysteroscopy, preferably office-based, is excellent for evaluating the endometrial cavity and endocervix; the false-negative rate is 3%<sup>29</sup> and it is more accurate than TVUS in detecting focal disease and also has greater specificity. A review of

65 articles that evaluated the role of hysteroscopy in 26,345 women determined that a positive hysteroscopy increased the probability of endometrial cancer to 71.8%, whereas a negative result reduced the probability of

cancer to 0.6%. De Jong et al<sup>30</sup> note that the sensitivity and specificity for the diagnosis of endometrial disease was 78% and 95.8%, respectively. For a positive result the pretest probability increased from 10.6% to 55.2%, and decreased to 2.8% with a negative result. All women having hysteroscopy should also have an endometrial biopsy, which provides a tissue diagnosis.

Hysteroscopy is more accurate in detecting intracavitary lesions, such as polyps and fibroids, than is blind endometrial biopsy alone. A recent study of 181 patients reported a sensitivity of 96.6% and a specificity of 100% when hysteroscopy was combined with endometrial biopsy.<sup>31</sup> Hysteroscopists sometimes find it difficult to distinguish between a proliferative, exaggerated endometrium and endometrial hyperplasia.<sup>32</sup> This is why it is critical to also perform endometrial biopsy with hysteroscopy. Theoretically, the specificity and positive predictive value of hysteroscopy in cases of abnormal uterine bleeding should be 100%. In practice, however, the false-negative rate is 2%–4%, and is the result of operator error in detecting abnormal endometrial lesions.

Hysteroscopic evaluation of the endometrium in postmenopausal women must be regimented. The hysteroscopist should systematically evaluate the endometrial height, surface and vascular architecture. Uterine disten-

tion media can include CO<sub>2</sub> or saline; however, both may be complementary and used concurrently. The endometrial thickness is usually <5 mm in the postmenopausal woman. The endometrial thickness can be assessed by pressing the tip of the hysteroscope into the endometrium. Without estrogen, there should be no compression or indentation of the endometrium; with estrogenic stimulation, there may be a wave-like surface with pseudopolypoid projections noted.

### Evaluation Findings: Clinical characteristics

Proper diagnosis depends upon the ability to accurately interpret findings from the diagnostic tools discussed above.

*Atrophy.* Endometrial atrophy is the most common cause of bleeding during menopause. Additionally, endometrial atrophy is common in perimenopausal women who use low-dose hormonal contraception. DepoProvera, DepoLupron, danazol, progesterone-only intrauterine systems or progesterone-only oral contraception can also be associated with atrophy. Atrophic endometrium has a translucent and porcelain appearance. The surface is smooth and dull. An atrophic endometrium may have pale endometrium covered by focal mucus-containing cysts, which, in turn, are covered by a thin endometrium. Diffuse or isolated petechial hemorrhages are frequently noted. Gland openings or cystic atrophy with openings adjacent to the myometrium are also noted. These gland openings appear translucent blue-gray. Because the endometrium is thin, the underlying muscle bundles of the myometrium and interlacing columns and recesses may produce diverticula.

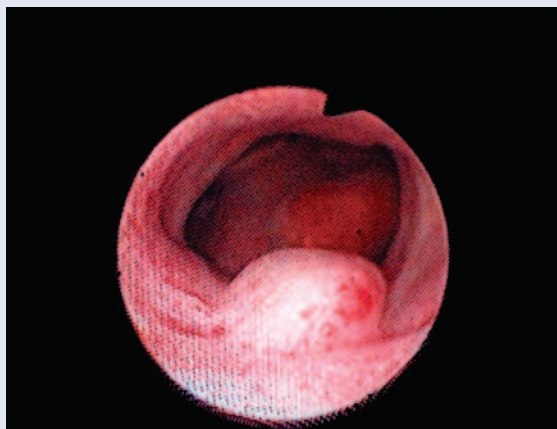
*Endometrial polyps.* Endometrial polyps are a frequent cause of bleeding. Polyps may vary in size, are usu-

ally single and are usually benign. Polyps respond to estrogen and tamoxifen with growth, whereas they are less sensitive to progesterone. As polyps grow, they can develop a pedicle and even protrude into the endocervix or into the vagina. Polyps share the same surface as the surrounding endometrium. Polyps may have a variety of colors, ranging from that which resembles the endometrium to red-yellow, and at the distal tip of the polyp an ecchymotic purple-blue color may be seen (Figure 5).

*Submucosal fibroids.* Intracavitary fibroids are firm and protrude from the endometrium. They are usually solitary, but may be accompanied by additional leiomyomas. In menopause, the endometrium covering the fibroid is thin. Blood vessels can be seen coursing over the surface of the myoma. On occasion, ulceration of the endometrium opposite the myoma can be seen. When the myoma is palpated with the distal tip of the hysteroscope, resistance is met and, unlike a polyp, the myoma cannot be pushed away from the hysteroscope. Intramural fibroids are unlikely sources of bleeding during menopause unless

the endometrium overlying them becomes markedly atrophic. The best view of an intramural fibroid appears when visualized from the internal os. Hysteroscopy is an excellent methodology to determine their number, size and location, and to determine if the patient has an intracavitary fibroid. A pedunculated fibroid can be hysteroscopically resected completely. The risk of sarcomatous changes is less than 1% in patients with uterine fibroids (Figure 6).

*Endometrial hyperplasia.* Making the diagnosis of endometrial hyperplasia in the postmenopausal woman is less difficult than in reproductive-age patients, who have a variable appearance of the endometrium due to hormonal fluctuations. Even so, the diagnosis of hyperplasia is the most often missed diagnosis with hysteroscopy, compared to SIS.<sup>33</sup> The most likely reason for “missing” the hyperplasia may be due to the techniques employed. When fluid distention or CO<sub>2</sub> compresses the endometrium, the endometrial projections of hyperplastic tissue are more difficult to discern. Making the diagnosis of endometrial hyperplasia requires close surveillance



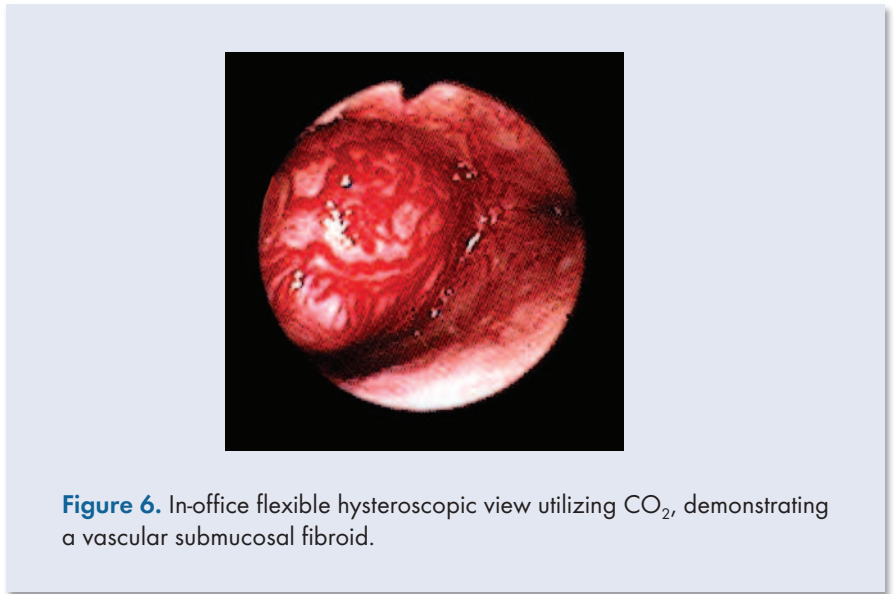
**Figure 5.** In-office flexible hysteroscopic view utilizing CO<sub>2</sub>. Note the endocervical myoma and an endometrial polyp arising from the left lateral wall.

of the tissue thickness, color, vasculature and consistency of the endometrium. Hyperplasia can be focal or global. Hyperplastic tissue has no organized structure and is an outgrowth of aberrant tissue, so it is easily friable and tears easily when touched with the hysteroscope. Abnormal-appearing endometrium may have focal lesions that include polyps. Additional cause for suspecting hyperplasia includes focal or papillary mucosal projections with or without gland cysts, an abnormal vascular network with atypical vessels, and crowded or abnormally-spaced gland openings.<sup>34</sup>

**Endometrial cancer.** Endometrial cancer has myriad appearances. Especially among postmenopausal women, the diagnosis is less likely to be missed. Boring, pale, atrophic, monotonous endometrial architecture best describes the postmenopausal endometrium. The chance of endometrial cancer increases when the hysteroscopist detects thickened, irregular endometrium; increased surface vascularity; friable cells; or when there is difficulty distending the endometrium.

Endometrial cancer requires histologic diagnosis; however, the index of suspicion can be raised when the topography of the endometrium is irregular or has focal lesions. Sugimoto et al<sup>35</sup> have noted a high sensitivity in detecting endometrial cancer when the following features are observed: papillary, polypoid, nodular or mixed endometrial growth demonstrating friable tissue, focal necrosis and atypical vessels.

**Tamoxifen-induced changes.** Endometrial surveillance of asymptomatic patients taking tamoxifen does not differ from that of women routinely using ET. Although most long-term users of tamoxifen will have an inactive endometrium, some will show increased endometrial thickness during conventional TVUS. In light of im-



**Figure 6.** In-office flexible hysteroscopic view utilizing CO<sub>2</sub>, demonstrating a vascular submucosal fibroid.

proved imaging, Goldstein et al<sup>36</sup> advocated SIS to monitor tamoxifen effects. With traditional TVUS, the endometrial thickness appears highly unusual and heterogeneous, and demonstrates centrally located uterine changes; if SIS is not performed, these unusual features can easily be overinterpreted. Unlike TVUS, SIS more accurately detects endometrial health and can determine if additional imaging is necessary. SIS can identify the subendometrial sonolucencies to the proximal myometrium. The abnormalities may represent abnormal adenomyomatous-like changes in the proximal myometrium that are microcysts. When viewed microscopically, the junction between the endometrium and myometrium is irregular and nonlinear, whereas in patients not receiving tamoxifen, the junction is linear.

Other ultrasonographic findings observed in patients taking tamoxifen (versus controls) consist of increased uterine volume and depth, greater endometrial thickness, increased incidence of endometrial polyps (36% vs 10%) and increased endometrial atrophy (28% vs 87%). A slight increase in the incidence of endometrial cancer,

of 2 to 3 cases per 1,000 women, has been noted among tamoxifen users.<sup>37</sup>

### Hormone Therapy and Abnormal Bleeding

Many women use HT for the alleviation of vasomotor symptoms, to decrease the risk of osteoporosis and improve urogenital atrophy. In the Women's Health Initiative study of over 8,000 women randomized to HT, about 40% of women complained of abnormal bleeding on the combined, continuous HT regimen utilizing conjugated equine estrogen 0.625 mg and medroxyprogesterone acetate 2.5 mg/daily.<sup>38</sup> Users of estrogen/progestosterone therapy (EPT) have a lower risk of endometrial cancer than do nonusers. Current recommendations include watchful waiting if vaginal bleeding occurs during the first 3 months of EPT. As discussed previously, in-office hysteroscopy or TVUS can be used to evaluate bleeding if it is persistent. Additionally, if patients are unwilling to continue therapy because of bleeding, then hysteroscopy or SIS can be recommended. As already stated, if TVUS only is used and the endometrial echo is < 5 mm, SIS, when available, should be performed

next to exclude intracavitary lesions when bleeding persists.

Patients on cyclic combined EPT should receive a minimum of 12–13 days of progestin therapy. Endometrial biopsy should be considered in patients who bleed before day 11 of a cyclic progestin regimen. If secretory or pseudodecidual changes are not evident, then additional progestin should be used. Patients using cyclical EPT who experience bleeding should be reassured if their bleeding occurs during the final 12–14 days of the progestin regimen or during the week following progestin withdrawal. If erratic bleeding occurs, then evaluation with in-office hysteroscopy or SIS should be undertaken.

Whichever HT formulation is chosen, approximately 30%–40% of women initiating HT will experience episodic or prolonged bleeding while on therapy.<sup>39</sup> In some cases, HT may produce bleeding in women who were previously asymptomatic. Earlier intervention with in-office hysteroscopy or SIS demonstrating endometrial atrophy or the presence of intracavitary lesions may allay many fears. If endometrial atrophy is detected, the patient can be reassured that bleeding will likely resolve with continued HT usage. Benign polyps and fibroids may continue to bleed, requiring hysteroscopic resection. Likewise, if a pre-malignant or occult malignancy is detected, prompt treatment with progesterone therapy or hysterectomy should be undertaken.

### Clinical Conundrums

For the woman who presents with PMB and who has marked cervical stenosis, evaluation can be challenging. Prior surgical procedures, such as laser conizations, loop excision and cold-knife biopsy, are associated with a 1%–40% risk of cervical stenosis.<sup>40</sup> But what can the clinician do in cases of profound cervical stenosis?

Traditionally, laminaria has been used for cervical dilation. But even the smallest laminaria cannot be placed with marked cervical stenosis. Oral or vaginal misoprostol is espe-

cially effective for cervical stenosis. Oral misoprostol (200–400 mcg 48 hours and, again, 8–12 hours before cervical dilation) is associated with increasing cervical softening and enhancing placement of a dilator.<sup>41</sup> Patients may have transient cramps, diarrhea or low-grade fever; however, misoprostol greatly facilitates performance of the procedure.

When misoprostol or laminaria attempts are not helpful, dilation of the cervix under ultrasound guidance should be considered. Ultrasound confirms proper placement of the instruments into the uterine cavity. Transabdominal ultrasound greatly improves the ability to guide an intrauterine catheter or endometrial pipelle biopsy device into the uterine cavity, and diminishes the likelihood of creating a false tract or perforation or abandoning the procedure. If this cannot be performed in the office, it can be performed under light sedation.<sup>42</sup>

Alternatively, flexible hysteroscopy may be more advantageous when a tortuous uterine cavity is encountered. If a 3-mm flexible hysteroscope can be placed into the cervix, it may be able to be navigated through the endocervix and into the uterine cavity to obtain visualization of the endometrium. The use of fluid or CO<sub>2</sub> also helps dilate the cervix. When marked cervical stenosis is encountered consider a shallow-cone loop electrosurgical excision procedure

to remove the stenotic cervical os. Rarely will the clinician need to resort to hysterectomy for marked cervical stenosis and PMB; however, in the presence of an abnormal ultrasound including a non-visualized endometrium, thickened endometrium or

### In some cases, HT may produce bleeding in women who were previously asymptomatic.

cervical dysplasia, hysterectomy is a reasonable option for managing abnormal bleeding when cervical stenosis is encountered.<sup>43</sup> In a retrospective study of patients with PMB who had cervical stenosis that precluded further evaluation and were subsequently treated by hysterectomy, 64% had benign pathology, 12% had cervical dysplasia (12%) and 4% had endometrial cancer.<sup>43</sup>

### Summary

Understanding the normal variations of perimenopausal bleeding is important. Likewise, postmenopausal women warrant thorough evaluation of the endometrium when PMB occurs. For both populations a low threshold for endometrial assessment is essential. Clinical tools used to evaluate the endometrium include endometrial biopsy, in-office hysteroscopy, TVUS and SIS. The use of cervical-softening agents, such as misoprostol, helps to make hysteroscopy, SIS and endometrial biopsies more comfortable, decreases the risk of uterine perforation or cervical lacerations, and facilitates cervical dilation. Hysteroscopy, particularly with small-diameter hysteroscopes, provides excellent imaging of the endocervix and endometrium in the office setting. When hysteroscopy is not available, TVUS is helpful in the initial triage of patients with abnormal uterine bleeding. TVUS, however,

does have limitations. When the endometrium is not well visualized with TVUS or bleeding continues despite normal endometrial parameters, hysteroscopy or SIS is advisable. The array of clinical tools available can direct therapy, and provide guidance for initiation of surgery or expectant management. ■

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## References

- Treloar AE. Menstrual cyclicity and the premenopause. *Maturitas* 1981;3:249-64.
- Seltzer VL, Benjamin R, Deutsch S. Perimenopausal bleeding patterns and pathologic findings. *J Am Med Womens Assoc* 1990;45:132-4.
- Landgren BM, Collins A, Csemiczky G, et al. Menopause transition: annual changes in serum hormonal patterns over the menstrual cycle in women during a nine-year period prior to menopause. *J Clin Endocrinol Metab* 2004;89:2763-69.
- Farquhar C, Ekeroma A, Furness S, Arroll B. A systematic review of transvaginal ultrasonography, sonohysterography and hysteroscopy for the investigation of abnormal uterine bleeding in premenopausal women. *Acta Obstet Gynecol Scand* 2003;82:493-504.
- Schwarzler P, Concin H, Bosch H, et al. An evaluation of sonohysterography and diagnostic hysteroscopy for the assessment of intrauterine pathology. *Ultrasound Obstet Gynecol* 1998;11:337-42.
- Erdem M, Bilgin U, Bozhurt N, et al. Comparison of transvaginal ultrasonography and saline infusion sonohysterography in evaluating the endometrial cavity in pre- and postmenopausal women with abnormal uterine bleeding. *Menopause* 2007;14:846-52.
- Breitkopf DM, Frederickson RA, Snyder RR. Detection of benign endometrial masses by endometrial stripe measurement in premenopausal women. *Obstet Gynecol* 2004;104:120-5.
- de Kroon CD, de Bock GH, Dieben SW, Jansen FW. Saline contrast hysterosonography in abnormal uterine bleeding: a systematic review and meta-analysis. *Br J Obstet Gynaecol* 2003;110:938-47.
- Astrup K, Olivarius Nde F. Frequency of spontaneously occurring postmenopausal bleeding in the general population. *Acta Obstet Gynecol Scand* 2004;83:203-7.
- Eitan R, Saenz CC, Venkatraman ES, et al. Pilot study prospectively evaluating the use of the measurement of preoperative sonographic endometrial thickness in postmenopausal patients with endometrial cancer. *Menopause* 2005;12:27-30.
- Marchetti M, Vasile C, Chiarelli S. Endometrial cancer: asymptomatic endometrial findings. Characteristics of postmenopausal endometrial cancer. *Eur J Gynaecol Oncol* 2005;26:479-84.
- Gredmark T, Kvint S, Havel G, et al. Histopathological findings in women with postmenopausal bleeding. *Br J Obstet Gynaecol* 1995;102:133-6.
- Karlsson B, Granberg S, Wikland M, et al. Transvaginal ultrasonography of the endometrium in women with postmenopausal bleeding—a Nordic multicenter study. *Am J Obstet Gynecol* 1995;172:1488-94.
- Goldstein SR, Nachtigall M, Snyder JR, Nachtigall L. Endometrial assessment by vaginal ultrasonography before endometrial sampling in patients with postmenopausal bleeding. *Am J Obstet Gynecol* 1990;163:119-23.
- Gull B, Karlsson B, Milsom I, Granberg S. Can ultrasound replace dilation and curettage? A longitudinal evaluation of postmenopausal bleeding and transvaginal sonographic measurement of the endometrium as predictors of endometrial cancer. *Am J Obstet Gynecol* 2003;188:401-8.
- Rose PG. Endometrial carcinoma. *N Engl J Med* 1996;335:640-9.
- Epstein E, Ramirez A, Skoog L, et al. Transvaginal sonography, saline contrast sonohysterography and hysteroscopy for the investigation of women with postmenopausal bleeding and endometrium > 5 mm. *Ultrasound Obstet Gynecol* 2001;18:157-62.
- Twu NF, Chen SS. Five-year follow-up of patients with recurrent postmenopausal bleeding. *Zhonghua Yi Xue ZaZhi (Taipei)* 2000;63:628-33.
- Chhieng DC, Elert P, Cohen JM, Cagiarella JF. Clinical significance of atypical glandular cells of undetermined significance in postmenopausal women. *Cancer* 2001;93:1-7.
- Epstein E, Ramirez A, Skoog L, et al. Dilation and curettage fails to detect most focal lesions in the uterine cavity in women with postmenopausal bleeding. *Acta Obstet Gynecol Scand* 2001;80:1131-36.
- Moodley M, Roberts C. Clinical pathway for the evaluation of postmenopausal bleeding with an emphasis on endometrial cancer detection. *J Obstet Gynaecol* 2004;24:736-41.
- Clark TJ, Barton PM, Coomarasamy A, et al. Investigating postmenopausal bleeding for endometrial cancer: cost-effectiveness of initial diagnostic strategies. *Br J Obstet Gynaecol* 2006;113:502-10.
- Shushan A, Revel A, Rojansky N. How often are endometrial polyps malignant? *Gynecol Obstet Invest* 2004;58:212-15.
- Savelli L, De Iaco P, Santini D, et al. Histopathologic features and risk factors for benignity, hyperplasia, and cancer in endometrial polyps. *Am J Obstet Gynecol* 2003;188:927-31.
- Smith-Bindman R, Kerlikowske K, Feldstein VA, et al. Endovaginal ultrasound to exclude endometrial cancer and other endometrial abnormalities. *JAMA* 1998;280:1510-17.
- Tsuda H, Kawabata M, Yamamoto K, et al. Prospective study to compare endometrial cytology and transvaginal ultrasonography for identification of endometrial malignancy. *Gynecol Oncol* 1997;65:383-6.
- Fleischer A, Wheeler JE, Lindsay I, et al. An assessment of the value of ultrasonographic screening for endometrial disease in postmenopausal women without symptoms. *Am J Obstet Gynecol* 2001;184:740-4.
- Gull B, Carlsson SA, Karlsson B, et al. Transvaginal ultrasonography of the endometrium in women with postmenopausal bleeding: is it always necessary to perform an endometrial biopsy? *Am J Obstet Gynecol* 2000;182:509-15.
- Clark TJ, Voit D, Gupta JK, et al. Accuracy of hysteroscopy in the diagnosis of endometrial cancer and hyperplasia: a systematic quantitative review. *JAMA* 2002;288:1610-21.
- De Jong P, Doel F, Falconer A. Outpatient diagnostic hysteroscopy. *Br J Obstet Gynaecol* 1990;97:299-303.
- Marchetti M, Litta P, Lanza P, et al. The role of hysteroscopy in early diagnosis of endometrial cancer. *Eur J Gynaecol Oncol* 2002;23:151-3.
- Fay TN, Khanem N, Hosking D. Out-patient hysteroscopy in asymptomatic postmenopausal women. *Climacteric* 1999;2:263-7.
- Widrich T, Bradley LD, Mitchinson A, Collins R. Comparison of saline infusion sonography with office hysteroscopy for the evaluation of the endometrium. *Am J Obstet Gynecol* 1996;174:1327-34.
- Garuti G, Sambruni I, Colonnelli M, Luerti M. Accuracy of hysteroscopy in predicting histopathology of endometrium in 1500 women. *J Am Assoc Gynecol Laparosc* 2001;8:207-13.
- Sugimoto O. Hysteroscopic diagnosis of endometrial carcinoma. A report of fifty-three cases examined at the women's clinic of Hyogo University Hospital. *Am J Obstet Gynecol* 1975;121:105-13.
- Goldstein SR, Nachtigall M, Snyder JR, Nachtigall L. Endometrial assessment by vaginal ultrasonography before endometrial sampling in patients with postmenopausal bleeding. *Am J Obstet Gynecol* 1990;163:119-23.
- Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer—report of the National Surgical Adjuvant Breast and Bowel Project. P-1 Study. *J Natl Cancer Inst* 1998;90:1371-88.
- Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-33.
- Ettinger B, Pressman A, Bradley C. Comparison of continuation of postmenopausal hormone replacement therapy: transdermal vs oral estrogen. *Menopause* 1998;5:152-6.
- Baldauf JJ, Dreyfus M, Ritter J, et al. Risk of cervical stenosis after large loop excision or laser conization. *Obstet Gynecol* 1996;88:933-8.
- Thomas JA, Leyland N, Durand N, et al. The use of oral misoprostol as a cervical ripening agent in operative hysteroscopy: a double-blind, placebo-controlled trial. *Am J Obstet Gynecol* 2002;186:876-9.
- Weiderpass E, Adami HO, Baron JA, et al. Risk of endometrial cancer following estrogen replacement with and without progestins. *J Natl Cancer Inst* 1999;1131-37.
- Newman C, Finan M. Hysterectomy in women with cervical stenosis. *J Reprod Med* 2003;48:672-6.