GENERAL GYNECOLOGY

The role of transvaginal ultrasound or endometrial biopsy in the evaluation of the menopausal endometrium

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All postmenopausal women with vaginal bleeding need endometrial assessment. Disposable suction piston biopsy devices have virtually replaced dilatation and curettage despite little scientific validation. In patients with known carcinoma, false-negative rates with such devices range from 2.5-32.4%. Large prospective studies have shown that an endometrial thickness ≤ 4 mm on transvaginal ultrasound in postmenopausal women with bleeding has a risk of malignancy of 1 in 917. Thus, in postmenopausal patients with bleeding, biopsy is not indicted when endometrial thickness is ≤ 4 mm. The significance of a thick endometrial echo in nonbleeding postmenopausal women has not been validated and need not require automatic tissue sampling.

Key words: Abnormal uterine bleeding, endometrial biopsy, endometrial thickness, postmenopausal bleeding, transvaginal ultrasound

Endometrial assessment is indicated in all postmenopausal women with any vaginal bleeding. Disposable suction piston devices have virtually replaced dilatation and curettage (D&C) despite little scientific validation. Transvaginal (TV) ultrasound (U/S) provides highly magnified images of endometrial contents. There is great confusion about the reliability of a thin distinct endometrial echo on TV U/S, especially in relationship to the reliability of a blind endometrial biopsy with a suction piston device. Significant prospective studies support the notion that a thin distinct endometrial echo ≤ 4 mm in a postmenopausal woman with bleeding will have an incidence of malignancy of about 1 in 1000. The sensitivity of suction piston biopsy done in patients with known carcinoma has reported false-negative rates ranging from 2.5-32.4%. The significance of a thick endometrial echo in nonbleeding postmenopausal women has not been validated. Of postmenopausal women, 10-17% have asymptomatic polyps. The incidence of malignancy in such polyps from reports cited have been 0%, 0%, 0%, and 2.4%. Finally, not all uteri lend themselves to a meaningful TV U/S determination because of things such as coexisting fibroids, axial uterus, preexisting surgery, or morbid obesity, all of which may impair the ability to use TV U/S as a reliable tool.

★ EDITORS' CHOICE ★

It has been almost 20 years since the first reports using TV U/S measurement of endometrial thickness in postmenopausal women with bleeding[1-3] have appeared. Although there have been many significant studies and many publications, it seems that there is still great confusion about the role of TV U/S in clinical treatment of such patients. The high negative predictive value of a thin distinct echo on TV U/S in postmenopausal women who present with bleeding is very different than thick measurements incidentally obtained on TV U/S in women who are asymptomatic (ie, no bleeding since the menopausal transition). This latter scenario has not been validated or adequately studied in a prospective fashion but data that do exist do not support the notion that such nonbleeding patients need to automatically have tissue obtained for histologic examination.

Furthermore, what exactly constitutes postmenopausal bleeding is not so easily defined. Menopause is defined as the final menstrual period. Obviously a woman has no way of knowing that the bleeding episode that has just occurred will be her last. Measurement of follicle-stimulating hormone (FSH) and estradiol levels are notoriously unreliable because, although they may indicate a lack of ovarian response to an increased pituitary FSH at that moment, resumption of some ovarian function in the ensuing months is not uncommon. In other words, the erratic function of the ovaries in late perimenopause often makes it difficult to label a woman's bleeding as definitively "postmenopausal." Generally, menopause has been defined as no bleeding for 12 months as a result of a depletion of ovarian follicles. Thus the patient who presents with clinical signs of menopause, with or without laboratory correlation of FSH levels, and then bleeds after 1 year of no bleeding, must be approached as "endometrial cancer until proven otherwise."

In the United States, cancer of the endometrium is the most common gynecologic cancer. In 2008 the American Cancer Society estimated that 41,520 cases of cancer of the uterine corpus would be diagnosed resulting in 8145 deaths.[4] Vaginal bleeding will be the presenting sign in more than 90% of postmenopausal patients with endometrial carcinoma.[5] The majority of patients with postmenopausal vaginal bleeding actually bleed secondary to atrophic changes of the vagina or endometrium.

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For Editors' Commentary, see Table of Contents

However, 1-14% of postmenopausal women with bleeding will have endometrial cancer depending on age and risk factors.[6-9] Thus, the clinical approach to postmenopausal bleeding requires prompt and efficient evaluation to exclude carcinoma.

Women who are not clearly menopausal with abnormal bleeding need evaluation as well. In fact, the American College of Obstetrician and Gynecologists Practice Bulletin No. 14 states that,[10] "There is a distinct increase in the incidence of endometrial carcinoma from ages 30-34 years (2.3/100,000 in 1995) to ages 35-39 (6.1/100,000 in 1995). Therefore based on age alone, endometrial assessment to exclude cancer is indicated in any woman older than 35 years who is suspected of having anovulatory uterine bleeding."

In addition, women < 35 years who have sufficient risk factors (eg, morbid obesity, polycystic ovary syndrome) may also require endometrial evaluation. Much of the evaluation of such nonmenopausal patients is similar to that in menopausal patients. The biggest difference (and this is fundamentally crucial) is that if one uses TV U/S or sonohysterography in women who still have endogenous ovarian function (ie, they are making estrogen) then any U/S evaluation must be timed to the end of the bleeding episode and be done as soon as possible after the bleeding ends when the endometrial thickness will be as thin as possible.[11] In postmenopausal women with no estrogen stimulation and thus no "cycling," U/S evaluation is not time sensitive and can be performed at any time. In the event a patient is on hormone therapy, this will depend on the type of hormone therapy used. In continuous combined hormone therapy there is no cycling and evaluation is not time sensitive. With sequential hormone therapy, there is development of the functionalis of the endometrium by estrogen and then sloughing after the administration of a progestogen. These patients should be evaluated like other cycling patients (ie, as soon as possible after the bleeding ends).

Historical background

Gynecologists have long approached postmenopausal bleeding as "endometrial cancer until proven otherwise." The traditional gold standard for endometrial evaluation was the D&C. First described in 1843,[12] its performance in the hospital became the most common operation performed on women in the world. As early as the 1950s, a review of 6907 curettage procedures[13] found the technique missed endometrial lesions in 10% of cases. Of these, 80% were polyps. A study of curettage before hysterectomy[14] found that in 16% of specimens less than one-quarter of the cavity was curetted, in 60% of specimens less than one-half of the cavity was curetted, and in 84% of specimens less than three-quarters of the endometrial cavity was effectively curetted.

In the 1970s, vacuum-suction curettage devices allowed sampling without anesthesia in an office setting. The most popular was the Vabra (Berkeley Medevices, Berkeley, CA) aspirator. This was 86% accurate in diagnosing cancer.[15] Subsequently, cheaper, smaller, less painful plastic catheters with their own internal pistons to generate suction became popular. One of these, the Pipelle (Unimar; Cooper Surgical, Trumbull, CT) device, had similar efficacy but better patient acceptance when compared with the Vabra.[16]

Pipelle gained widespread acceptance with very little validation. It was first described by Cornier[17] in 1984 in an article entitled "The Pipelle: a disposable device for endometrial biopsy." Subsequently, from 1988-1991, there were 8 articles, of which 7 evaluated Pipelle (often compared with other methods) for timed endometrial biopsy in the luteal phase of the menstrual cycle as part of an infertility evaluation–something no longer used. An article by Kaunitz et al[16] compared Pipelle with Vabra aspiration in 56 patients and found that the final diagnosis was concordant in 50 (89%) of 56. They concluded that Pipelle had similar efficacy to Vabra but much higher patient acceptability (ie, comfort). In 1991 Stovall et al[18] performed Pipelle on 40 patients with known carcinoma in the clinic before their scheduled hysterectomy. They identified endometrial carcinoma in 39 of 40, yielding a sensitivity of 97.5%. These findings were widely advertised throughout the early 1990s and suction devices with their own internal pistons were rapidly adopted as the method of choice for endometrial evaluation. Compared with D&C and the Vabra aspirator such suction piston biopsy instruments were safe, easy, inexpensive, and resulted in less patient discomfort or need for anesthesia or analgesia. It is easy to understand why clinicians rapidly adopted this as the method of choice for endometrial evaluation. The device has become so popular that, although many clinicians may use other brands, the word "Pipelle" has become synonymous with suction piston biopsy instruments just as we often go to the "Xerox" machine (Xerox Corporation, Norwalk, CT) even though our copier may be another brand or we ask for a "Kleenex" (Kimberly-Clark Corporation, Irving, TX) even though our tissue may come from another manufacturer.

Suction piston biopsy devices have several important limitations. First, such devices sample only a small surface of the endometrial cavity. Rodriguez et al[19] did a pathologic study of 25 hysterectomy specimens. The percentage of endometrial surface sampled by the Pipelle device was 4% vs 41% for the Vabra aspirator.

In addition, the sensitivity of such suction piston biopsy devices is quite variable. In other studies, for patients with known malignancies who underwent Pipelle biopsy before hysterectomy, the diagnosis of cancer was missed in 2 (7.6%) of 26[20] and in 12 (32.4%) of 37,[21] not nearly as reliable as the original work by Stovall et al.[18]

The significance of such sampling's limitations is highlighted in another study by Guido et al.[22] They also studied Pipelle biopsy in patients with known carcinoma undergoing hysterectomy. Among 65 patients a Pipelle biopsy provided tissue adequate for analysis in 63 (97%). Malignancy was detected in only 54 (83%) patients. Thus there was a 17% false-negative rate in these patients with

known carcinoma! However, when the uterine specimens were analyzed, of the 11 cases that were missed, in 3 the tumor occupied ≤ 5% of the surface area of the cavity, in another 4 the tumor occupied 6-25% of the surface area of the cavity, and in the remaining 4 the tumor occupied 26-50% of the cavity. When the tumor involved > 50% of the cavity, Pipelle missed none. This was true in only 46% (30/65) of patients. Of 11 patients with tumors confirmed to polyps, Pipelle missed 5. Because tumors localized in a polyp or a small area of endometrium may go undetected, the authors in that study concluded that the "Pipelle is excellent for detecting global processes in the endometrium."

In another study,[23] Pipelle aspiration biopsy was performed in 135 premenopausal patients before curettage. Thirteen (10%) patients had different histologic results on Pipelle biopsy as compared with curettage. Five of these patients had polyps, of which Pipelle sampling missed 3. In total, 18 patients had hyperplasia, of which Pipelle sampling missed the diagnosis in 7 (39%), thus underscoring the often focal nature of that pathological process (Figures 1-3).

Finally, a similar study done on patients with known endometrial carcinoma but using the Z sampler (Zinanti, Chatsworth, CA) brand of suction piston biopsy device[24] correctly identified only 66 of 80 patients yielding a sensitivity of 82.5% (ie, 17.5% of cancers were missed).

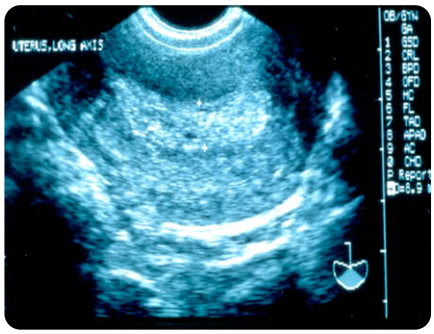
From these data it seems that undirected sampling, whether through curettage or various types of suction aspiration, will often result in erroneous conclusions especially in cases in which the abnormality is not global but focal (polyps, focal hyperplasia, or carcinoma involving small areas of the uterine cavity).

TV U/S in postmenopausal bleeding: historical perspective

TV U/S was introduced in the mid 1980s. It uses higher frequency transducers in closer proximity to the structure being studied. This yields a degree of image magnification that has been termed "sonomicroscopy," in which structures that could not be appreciated previously with a naked eye can be discerned. For instance, cardiac pulsations are clearly visible within a 3-mm embryo at 45 days from the last menstrual period. If you could hold this structure in your hand at arms length you could not appreciate cardiac pulsations within a 3-mm embryo. Atrophic endometrium, as expected in a postmenopausal patient who is on no hormone replacement therapy, will appear on U/S as a thin "pencil line" echogenicity (Figure 4). This is surrounded by an intact hypoechoic "halo." This thin echogenic line merely represents the interface between 2 sides of atrophic basal endometrium. The basalis of the endometrium itself is 1 cell layer thick in this stage. It is unclear exactly what causes the echogenicity that we routinely image as this "interface."

TV U/S has been studied as an inexpensive noninvasive way to directly visu-

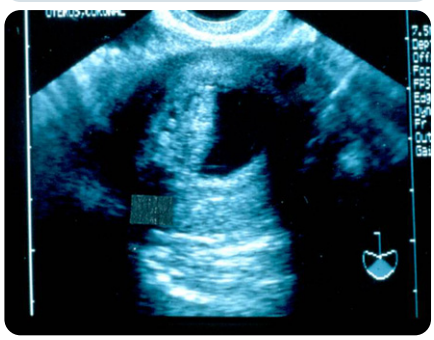
FIGURE 1
Unenhanced transvaginal sonogram



Long-axis transvaginal sonogram of endometrium in patient with bleeding and echo measurement of 8.9 mm.

Goldstein. The role of TV U/S or endometrial biopsy in the evaluation of the menopausal endometrium. Am J Obstet Gynecol 2009.

FIGURE 2
Saline infusion sonohysterography



Sonohysterogram of patient in Figure 1 showing right side of endometrial cavity with abundant thick tissue whereas left side is thin.

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FIGURE 3
Hysteroscopic evaluation

Hysteroscopic view of endometrium of patient depicted in Figures 1 and 2. Right side of endometrial cavity is filled with tissue with complex atypical hyperplasia histopathology. Remainder of cavity was inactive.

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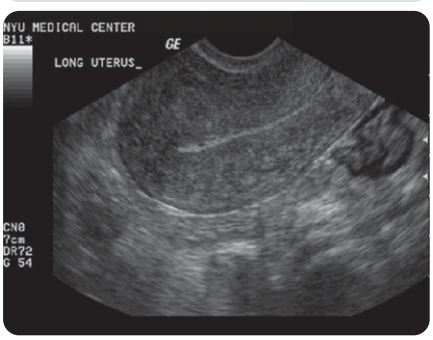
FIGURE 4
Thin distinct endometrial echo



Long-axis transvaginal sonogram of postmenopausal patient with history of staining. Endometrial echo here has thin "pencil line" appearance.

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alize the endometrial cavity. The first publication on this was by Nasri and Coast.[1] They studied 93 women with postmenopausal bleeding and correlated between U/S and histology. Of cases with endometrial measurements of 1-5 mm, 100% (51/51) had inactive endometrium. There were 6 patients with endometrial cancer. The endometrial measurements ranged from 8-38 mm. When endometrial fluid was present they incorporated the fluid and the anterior and posterior endometrial measurements in a combined total measurement.

The next study[2] was done by the current author and coworkers. The hypothesis for this pilot study came from the fact that in postmenopausal women who had no bleeding, endometrial measurement on TV U/S was usually quite thin. This seemed to be compatible with the lack of development of the functionalis because of no stimulation of estrogen. Furthermore, in patients with endometriosis in whom danazol or newer gonadotropin-releasing hormone agonists were used, the endometrium virtually always appeared as a thin white "pencil line" structure. The hypothesis was that if TV U/S could reliably identify those patients with bleeding who lacked significant tissue, then perhaps these patients could be spared invasive endometrium sampling and its inherent risks, discomfort, and expense. Of 30 patients with postmenopausal bleeding, all those with endometrial thickness $\leq$ 5 mm had inactive endometrium or scant cellular material on biopsy whereas when the endometrium measured $\geq$ 6 mm, all pathologies were encountered. The sole patient with endometrial cancer in that study had an endometrial thickness that measured 8 mm.

Varner et al[3] studied 80 women, of whom 65 were asymptomatic and 15 had postmenopausal bleeding. They used either a Pipelle aspiration or Novak curette (Jarit, Tuttlingen, Germany). All 60 (100%) women with endometrial measurement of $\leq$ 4 mm had inactive endometrium on biopsy. Five women had an endometrial measurement of 5 mm. Of these biopsy specimens, 2 were inactive, 1 proliferative, 1 hyperplastic, and 1 was carcinoma (although none of these had photographs shown). Their largest measurement associated with inactive endometrium was 5 mm. The thickness of the endometrium in the 2 cancers measured 5 and 9 mm, respectively.

Granberg et al[25] studied 205 women with postmenopausal bleeding. There were no cases of cancer with an endometrial echo $<$ 9 mm. The mean thickness for endometrial cancer was 15.2 mm (range, 9-25 mm). The mean thickness for atrophic changes was 3.4 mm (range, 1-15), although 150 of 157 were $\leq$ 5 mm. They concluded that curettage could be avoided in postmenopausal women with bleeding and an endometrial echo of $\leq$ 5 mm and not miss any endometrial cancer and still reduce the number of D&Cs by 70%.

TV U/S: validation of early studies

Since those early studies a number of large multicenter trials have taken place. In the Nordic trial, which included 1168 postmenopausal women with bleeding and TV U/S echo $\leq$ 4 mm, no cancers were detected on curettage.[26] An Italian multicenter study of 930 women with postmenopausal bleeding[27] had an incidence of endometrial cancer of 11.5%. When the endometrial echo was $\leq$ 4 mm there were 2 cases of endometrial cancer (negative predictive value = 99.79%. When the endometrial echo was $\leq$ 5 mm there were 4 cases of endometrial cancer (negative predictive value = 99.57%). When the endometrial echo was $\leq$ 5 mm there were no cases of complex hyperplasia. Gull et al[28] evaluated 163 women with postmenopausal bleeding and an endometrial echo $\leq$ 4 mm and found only 1 (0.6%) cancer. Epstein and Valentin[29] studied 97 women with postmenopausal bleeding and endometrial echo $<$ 5 mm and there were no cancers. In another Scandinavian study of 394 women with postmenopausal bleeding, there were no cases of cancer as compared with curettage, and through follow-up for 10 years, if the endometrial echo was $<$ 4 mm.[30]

Is endometrial biopsy still necessary?

If we combine these previous 5 studies of women with postmenopausal bleeding and endometrial echo $\leq$ 4 mm on TV U/S, there were only 3 cancers in 2752 patients. Stated another way, a patient with postmenopausal bleeding and a thin distinct endometrial echo $\leq$ 4 mm has a chance of having endometrial cancer of 1 in 917. It is useful to contrast that with the false-negative rates of blind endometrial sampling in patients with known carcinoma cited previously.

Furthermore, if one did perform biopsies on such patients who have such a thin distinct endometrial echo on TV U/S, what would the expected findings be? Endometrial sampling resulting in findings of tissue insufficient for diagnosis is common. In a study of 97 consecutive patients with postmenopausal bleeding evaluated by TV U/S and endometrial biopsy, only 82% of the patients with an endometrial thickness $<$ 5 mm (n = 45) had a successful Pipelle biopsy completed.[31] Of these patients, only 27% gave a sample adequate for diagnosis. There was no correlation with parity or cavity length. In other studies of patients with postmenopausal bleeding, the range of sampling failure with Pipelle was 0-54%.[32]

Limitations of TV U/S

Not all uteri lend themselves to a meaningful examination yielding a reliable endometrial echo.[33] In a study of 433 perimenopausal women with abnormal uterine bleeding,[34] a reliable endometrial echo on TV U/S could not be visualized in 10% of patients, causing those authors to proceed to saline infusion sonohysterography.

Because U/S will not yield a tissue diagnosis, it is important that it be appropriately performed and documented. If one angles the transducer long enough, eventually one can almost always find something linear and white, freeze the frame, place calipers, and call this the "endometrial echo" (Figure 5). A well-defined endometrial echo should be seen taking off from the endocervical canal. It should be distinct. Often fibroids, previous surgery, marked obesity, or an axial uterus may make visualization suboptimal. If so, it is perfectly acceptable, and, in fact, appropriate to conclude "endometrial echo not well visualized." In these cases, the U/S can not be relied on

to exclude pathology. Saline infusion sonohysterography or hysteroscopy are both appropriate next steps in the endometrial evaluation of such patients, if such patients have a history of bleeding.

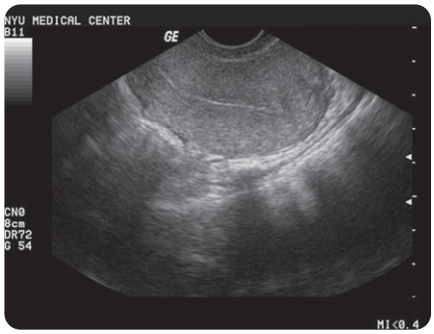
Another important consideration, in addition to measured endometrial thickness, is the texture of the endometrium. If it is heterogeneous and irregular, this may be a more important determinant than simply absolute thickness. Furthermore, it should be stressed that these endometrial measurements have to be made on a long-axis view perpendicular to the endometrial echo. The coronal view will be fraught with error because this may be tangential and not perpendicular. Also, carcinomas, hyperplasias, and polyps are often focal. It is not sufficient to simply produce a single long-axis view that is then measured. Multiple 2-dimensional views in the long axis from cornua to cornua are mandatory in an attempt to recreate 3-dimensional anatomy and avoid missing changes that may be focal. Fluid instillation sonohysterography can also be very helpful, and proof that a pathologic process is symmetric (ie, "global" and not focal) should precede any type of blind office sampling.

TV U/S in nonbleeding postmenopausal patients

The increasing use of imaging in a variety of clinical situations has led to the identification of thick endometrial findings in asymptomatic (ie, nonbleeding) postmenopausal women. What is the significance of such a finding and how should it be handled clinically?

The "endometrial echo" is very much today[33] where the postmenopausal cystic ovary was in the early to mid 1980s. On the basis of the work by Barber and Graber[35] an entire generation of gynecologists were trained and believed that a palpable postmenopausal ovary was "cancer until proven otherwise." When real-time U/S began to be widely used, many postmenopausal women with simple ovarian cysts were discovered and virtually always operated on. Early articles[36,37] began to support the notion that simple cysts of postmenopausal ovaries are invariably benign and do not require surgical intervention. This indeed has become the norm.[38] In fact 10-17% of asymptomatic postmenopausal women[39] will have simple cystic structures when scanned with modern TV U/S equipment. The postmenopausal cystic adnexal mass was an example of how we cannot apply new technologies to old principles of clinical management. New studies must be performed before recommendations can be made. Postmenopausal cystic adnexal masses are not the same as palpably enlarged ovaries. All Barber and Graber[35] ever said was a normal ovary should no longer be palpable and, if it is, it is not secondary to functional or dysfunctional change. Now that abundant study has shown that simple cysts: (1) in postmenopausal women are invariably benign; and (2) are quite prevalent, we can intelligently incorporate TV U/S into clinical treatment of such patients. No prospective studies have ever been done to validate what is the significance of a thick endometrial echo discovered incidentally on a sonogram in a healthy nonbleeding patient. The response that such patients must have tissue sampling is not founded on any evidence. We know that a majority of women will have some leiomyomas in their lifetime. They shrink but do not disappear after menopause. Those that are submucous may appear on TV U/S to be a thickened endometrial echo. In addition 10-17% of the population in that age group would be expected to have asymptomatic (ie, nonbleeding inactive) polyps.[40-42]

FIGURE 5



Long-axis transvaginal sonogram showing atrophic endometrial cavity. Note endometrial echo is seen emanating from endocervical canal.

Goldstein. The role of TV U/S or endometrial biopsy in the evaluation of the menopausal endometrium. Am J Obstet Gynecol 2009.

What is the risk of malignancy in such polyps in nonbleeding patients? Fernandez-Parra et al[43] removed 117 polyps in postmenopausal women without bleeding and none had a malignancy. They also discussed the importance of distinguishing endometrial carcinoma with polypoid growth from carcinoma arising in a polyp. They put forth the idea that for a polyp to be the origin of endometrial carcinoma both the base of the polyp and the surrounding endometrium must be benign.

Shushan et al[44] studied 300 consecutive women with endometrial polyps who underwent hysteroscopic removal. A total of 73 (24.3%) patients were asymptomatic and their polyps were incidentally discovered. They combined perimenopausal and postmenopausal patients. All asymptomatic polyps in their series were benign. In addition, their rate of malignancy or complex atypical hyperplasia in polyps of patients with bleeding was 1.6%.

Lieng et al[45] found malignancies or complex atypical hyperplasia in 2 (2.6%) of 74 postmenopausal women who were asymptomatic. The limitation of this study was that it was a retrospective review of their surgical database and it is unclear why these asymptomatic patients were selected for surgery.

Lev-Sagie et al[46] performed operative hysteroscopy on 82 postmenopausal women who had incidental findings of endometrial "thickening." There were no cases of complex hyperplasia or carcinoma. There were 67 inactive polyps, 7 submucosal myomas, 6 atrophic endometria, 1 proliferative endometrium, and 1 polyp with simple hyperplasia. Their total complication rate was 3.6% (2 perforations, and 1 difficult intubation).

Summary

In summary, in postmenopausal women with bleeding, TV U/S (and sonohysterography when necessary) is a simple, inexpensive, well-tolerated office procedure to triage patients to: (1) no anatomic endometrial pathology (treated expectantly); (2) globally thickened endometrial tissue (candidates for blind sampling); or (3)

abnormally thickened tissue but focal (including polyps and nonglobal pathology) in need of visually directed sampling. In women without bleeding incidental abnormal findings on various imaging studies have not been scientifically evaluated. Benign quiescent anatomic structures may be common, never before detected, and easily seen with the improved resolution of all imaging modalities. Additional testing and evaluation has not been shown to be necessary or clinically relevant and in some cases may result in more harm to patients than good. Obviously decisions about what to do with incidental unexpected findings should be made on a case-by-case basis depending on a multitude of factors. A thin distinct endometrial echo on TV U/S in a woman with bleeding has a very high negative predictive value, but a thick endometrial echo in a woman without bleeding is not validated and does not require automatic tissue sampling. ■

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