Endovaginal Ultrasound to Exclude Endometrial Cancer and Other Endometrial Abnormalities

Rebecca Smith-Bindman; Karla Kerlikowske; Vickie A. Feldstein; et al.


http://jama.ama-assn.org/cgi/content/full/280/17/1510

Correction Contact me if this article is corrected.

Citations This article has been cited 170 times.

Contact me when this article is cited.

Topic collections Radiologic Imaging; Review; Ultrasonography

Contact me when new articles are published in these topic areas.

Related Articles published in the same issue Vaginal Ultrasonography to Evaluate Postmenopausal Bleeding


Subscribe
http://jama.com/subscribe

Permissions
permissions@ama-assn.org
http://pubs.ama-assn.org/misc/permissions.dtl

Email Alerts
http://jamaarchives.com/alerts

Reprints/E-prints
reprints@ama-assn.org

Downloaded from www.jama.com at University of Alabama-Birmingham on June 12, 2008
Endovaginal Ultrasound to Exclude Endometrial Cancer and Other Endometrial Abnormalities

Rebecca Smith-Bindman, MD; Karla Kerlikowske, MD; Vickie A. Feldstein, MD; Leslee Subak, MD; Juergen Scheidler, MD; Mark Segal, PhD; Richard Brand, PhD; Deborah Grady, MD

**Context.**—Postmenopausal vaginal bleeding is a common clinical problem. Endovaginal ultrasound (EVUS) is a noninvasive diagnostic test that may help determine which women should undergo endometrial biopsy.

**Objective.**—To determine the accuracy of EVUS in detecting endometrial disease in postmenopausal women with vaginal bleeding according to hormone replacement use.


**Study Selection.**—Studies were included if they prospectively collected EVUS measurements of endometrial thickness prior to obtaining endometrial tissue for histologic evaluation in postmenopausal women with vaginal bleeding. Of 85 studies that included data on EVUS and endometrial histology, 35 were included in the meta-analysis and included 5892 women.

**Data Extraction.**—Articles were reviewed and independently selected and abstracted by 2 reviewers. Disagreement was resolved by consensus.

**Data Synthesis.**—The overall summary mean weighted estimates of sensitivity and specificity were calculated for thresholds of endometrial thickness from 3 to 10 mm. Using a 5-mm threshold to define abnormal endometrial thickening, 96% (95% confidence interval [CI], 94%-98%) of women with cancer had an abnormal EVUS result, whereas 92% (95% CI, 90%-93%) of women with endometrial disease (cancer, polyp, or atypical hyperplasia) had an abnormal result. This did not vary by hormone replacement use. However, the number of women with normal histology who had an abnormal EVUS result did vary by hormone replacement use. In women who were not using hormone replacement therapy, 593 (8%) with normal histological findings had an abnormal EVUS result (specificity, 92%; 95% CI, 90%-94%), whereas 1544 (23%) using hormone replacement therapy had an abnormal EVUS result (specificity, 77%; 95% CI, 75%-79%). For a postmenopausal woman with vaginal bleeding with a 10% pretest probability of endometrial cancer, her probability of cancer is 1% following a normal EVUS result.

**Conclusion.**—Endovaginal ultrasound has a high sensitivity for detecting endometrial cancer and other endometrial disease and can reliably identify postmenopausal women with vaginal bleeding who are highly unlikely to have significant endometrial disease so that endometrial sampling may be unnecessary.

JAMA. 1998;280:1510-1517

ENDOMETRIAL cancer is the fourth most common malignancy in women in the United States, with more than 36 000 cases and 6300 deaths occurring annually.1 The majority of women with endometrial cancer are postmenopausal and present with vaginal bleeding. In most women with abnormal vaginal bleeding, endometrial sampling with an endometrial biopsy or dilatation and curettage is performed. Endometrial cancer has been detected in 5% to 60% of postmenopausal women with vaginal bleeding, depending on age and other risk factors.2-5 Office-based endometrial biopsy techniques are uncomfortable,6,7 cannot be performed or are nondiagnostic in 2% to 28% of attempts,4,6,8,11,12 and often yield an inaccurate diagnosis, particularly for women with endometrial polyps.13,14

For editorial comment see p 1529.

During the last decade, endovaginal ultrasound (EVUS) has become widely used to evaluate the endometrium in postmenopausal women with vaginal bleeding. Endovaginal ultrasound uses an ultrasound probe that is placed directly in the vagina to obtain detailed images of the endometrium. Thin endometrium is generally considered normal, whereas thickened endometrium may represent cancer, hyperplasia, or polyps. The chief goal of an EVUS examination of the endometrium is to exclude pathological conditions and thereby make endometrial sampling unnecessary.

Many published studies have assessed the accuracy of EVUS in evaluating the endometrium for malignancy.8,11,13,14 While it has been suggested that cancer can be excluded with a high degree of confidence when the endometrial thickness is less than 3 mm, a few studies have reported cancer in women with a thin endo-
Endovaginal Ultrasound to Exclude Endometrial Cancer—Bindman et al

JAMA, November 4, 1998—Vol 280, No. 17

Endometrial measurement. However, most studies of the diagnostic accuracy of EVUS have been small and included few women with cancer. Additionally, studies applied different thresholds of endometrial thickness for calling an EVUS result abnormal and many have not reported the results separately in women receiving hormone replacement therapy.

To enhance the precision of estimates of the accuracy of EVUS, we conducted a critical review of the literature and used meta-analytic techniques to determine the accuracy of EVUS in diagnosing endometrial pathological conditions in postmenopausal women with vaginal bleeding according to hormone replacement therapy use. Our main goal was to determine if EVUS can reliably identify women who are highly unlikely to have significant endometrial disease and therefore need no further evaluation.

METHODS

Data Sources

We performed a literature search using the MEDLINE database of all studies published from January 1966 through November 1996 and manually searched bibliographies of published articles. MEDLINE search terms included endometrium, endometrial cancer, ultrasound, endovaginal ultrasound, transvaginal ultrasound, vaginal bleeding, dilation and curettage, and endometrial biopsy. Review articles, letters, case reports, and comments were excluded. English-language and non–English-language articles were included. We identified 85 studies that included data on EVUS and endometrial sampling. Of these, 12 were in German, 5 Italian, 3 French, 1 Chinese, 1 Dutch, and the remainder in the English language.

Study Selection

Articles were independently selected and reviewed by 2 reviewers. Studies that prospectively evaluated EVUS on patients prior to obtaining endometrial tissue (endometrial biopsy, dilation and curettage, or hysterectomy) were included. Retrospective studies, studies with selective histological sampling, studies that reported results pooled for premenopausal and postmenopausal women, and studies that measured endometrial thickness following tissue sampling were excluded. In addition, studies that evaluated EVUS only in asymptomatic women, women receiving tamoxifen, and women with known endometrial cancer were excluded. Studies not reporting endovaginal thickness measurements were excluded. When we could not extract data from published articles, we wrote to the corresponding author to obtain additional information (18 authors, 5 of whom responded). Additional nonpublished results were obtained from 2 authors, and these are included in our analysis with published results by the same authors.

For studies that resulted in multiple publications, data from the most recent publication were used.

Data Abstraction

We defined endometrial thickness as the width of the combined thickness of the anterior and posterior sides of the endometrium. When a single-wall measurement was reported, we doubled the measurement. Three outcomes were considered: cancer, benign endometrial abnormalities (atypical and complex hyperplasia or polyp), and normal (atrophic, normal). Endometrial disease was defined as including cancer and benign endometrial abnormalities. Within each study, cases of cervical and cervical polyps were excluded. For each outcome, 2 authors abstracted and recorded the number of true-positive, false-positive, true-negative, and false-negative cases using all reported thickness thresholds (3, 4, 5, 6, 7, 8, 9, and 10 mm). We also abstracted the mean endometrial thickness among women with atrophic endometrium, hyperplasia or polyps, and cancer. For each study we also recorded mean age, the number of women using hormone replacement therapy, the number of women with vaginal bleeding, frequency of the ultrasound probe, whether fluid within the endometrial cavity was included, and whether “≤” or “<” was considered as the dividing point between normal and abnormal. We also recorded the number of women who could not tolerate or who had a nondiagnostic EVUS result. Discrepancies among reviewers were resolved by consensus.

Data Synthesis

For each study, the sensitivity, specificity, and exact 95% confidence intervals (CIs) were calculated for all EVUS thickness measurements. When studies did not explicitly state hormone replacement therapy use, additional nonpublished information (18 authors, 5 of whom responded) we analyzed these articles with those that included women using hormone replacement therapy, as we assumed some women may have been using hormone replacement therapy. In the studies that included women using hormone replacement therapy, the percentage of these women varied from 0% to 100%.

Studies used endometrial thickness measurements of 3 to 10 mm to define an abnormal EVUS test result. Before we combined the results across studies, we tested whether there was a trade-off between sensitivity and specificity for each thickness threshold. If we found there was no correlation of sensitivity and specificity within any of the individual thickness measurements used to define abnormal (for example, ≤5 mm) across the different studies. Therefore, we calculated mean weighted pooled estimates of sensitivity and specificity for each threshold, for any endometrial disease, and for cancer alone.

The summary estimates were calculated as a weighted average. Individual study findings were weighted by sample size. For example, the summary weighted sensitivity was calculated as the sum of the sensitivities reported for each study multiplied by the number of subjects in that study, divided by the total number of subjects in all of the studies. Sensitivity for cancer was weighted by the number of cases of cancer, sensitivity for endometrial disease was weighted by the number of endometrial abnormalities, and specificity was weighted by the number of normal women without endometrial abnormalities. The 95% CIs for the mean weighted results were calculated using exact methods.

A test for homogeneity was performed to evaluate the consistency of findings across studies. We used the CIs of the individual study findings to determine if the results were homogeneous; if the 95% CI from a study did not overlap the weighted summary point estimate, the result of that study was considered heterogeneous.

Possible reasons for heterogeneity, such as whether the study was published in the English language or a non–English language, use of hormone replacement therapy, patient symptoms, whether fluid within the endometrial cavity was included or excluded in determining endometrial thickness, and specialty of the examiner were studied by stratifying the summary estimate according to these factors to determine if homogeneity improved.

Positive and negative likelihood ratios were calculated for each endometrial thickness. The posttest risk of endometrial disease was calculated using the 5-mm-thickness threshold, varying the pretest risk of disease from 1% to 50%. A summary receiver operating characteristic curve (ROC) was generated using the data from all thresholds using the method of Moses and colleagues to combine the results across the range of endometrial thicknesses. We tested for differences between the summary ROC curves of women who used hormone replacement therapy and women who did not. We also tested for differences between the summary ROC curves of women who did not tolerate or who had a nondiagnostic EVUS result. Discrepancies among reviewers were resolved by consensus.

JAMA, November 4, 1998—Vol 280, No. 17

Endovaginal Ultrasound to Exclude Endometrial Cancer—Bindman et al

©1998 American Medical Association. All rights reserved.
Table 1.—Prospective Studies Comparing Endovaginal Ultrasound Measurements With Endometrial Histology in Postmenopausal Women Included in Meta-analysis

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Vaginal Bleeding</th>
<th>Hormone Replacement Therapy*</th>
<th>Endometrial Disease†</th>
<th>Cancer</th>
<th>Endometrial Thickness Cutoffs, mm‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abu Hmeidan et al,§ 1992</td>
<td>545 (100)</td>
<td>NS</td>
<td>274 (50)</td>
<td>86 (16)</td>
<td>5</td>
</tr>
<tr>
<td>Aleem et al,§ 1995</td>
<td>42 (33)</td>
<td>0</td>
<td>23 (55)</td>
<td>14 (33)</td>
<td>8</td>
</tr>
<tr>
<td>Auslander et al,§ 1993</td>
<td>134 (100)</td>
<td>0</td>
<td>66 (49)</td>
<td>16 (12)</td>
<td>3, 4, 5, 6, 7, 8, 10</td>
</tr>
<tr>
<td>Batol et al,§ 1992</td>
<td>120 (100)</td>
<td>0</td>
<td>22 (18)</td>
<td>8 (7)</td>
<td>5, 10</td>
</tr>
<tr>
<td>Brotmann et al,§ 1993</td>
<td>54 (100)</td>
<td>0</td>
<td>32 (59)</td>
<td>10 (19)</td>
<td>6, 8</td>
</tr>
<tr>
<td>Caicciarelli et al,§ 1994</td>
<td>45 (100)</td>
<td>20 (44)</td>
<td>23 (51)</td>
<td>4 (9)</td>
<td>5</td>
</tr>
<tr>
<td>Chan et al,§ 1994</td>
<td>67 (100)</td>
<td>0</td>
<td>29 (43)</td>
<td>17 (25)</td>
<td>4, 5, 6, 7</td>
</tr>
<tr>
<td>Denghardt et al,§ 1991</td>
<td>37 (100)</td>
<td>NS</td>
<td>37 (27)</td>
<td>37 (100)</td>
<td>6</td>
</tr>
<tr>
<td>Dijkmuisen et al,§ 1996</td>
<td>69 (100)</td>
<td>0</td>
<td>31 (45)</td>
<td>8 (12)</td>
<td>6, 8, 10</td>
</tr>
<tr>
<td>Dorrun et al,§ 1993</td>
<td>100 (100)</td>
<td>12 (12)</td>
<td>25 (25)</td>
<td>15 (15)</td>
<td>5</td>
</tr>
<tr>
<td>Goldstein et al,§ 1995</td>
<td>28 (100)</td>
<td>18 (64)</td>
<td>6 (21)</td>
<td>1 (4)</td>
<td>5</td>
</tr>
<tr>
<td>Granberg et al,§ 1994</td>
<td>45 (100)</td>
<td>20 (44)</td>
<td>23 (51)</td>
<td>4 (9)</td>
<td>5</td>
</tr>
<tr>
<td>Hanggi et al,§ 1995</td>
<td>89 (100)</td>
<td>0</td>
<td>25 (28)</td>
<td>21 (24)</td>
<td>5</td>
</tr>
<tr>
<td>Karlsson et al,§ 1993</td>
<td>105 (100)</td>
<td>NS</td>
<td>35 (33)</td>
<td>15 (14)</td>
<td>5</td>
</tr>
<tr>
<td>Karlsson et al,§ 1994</td>
<td>51 (100)</td>
<td>NS</td>
<td>35 (69)</td>
<td>0 (0)</td>
<td>4</td>
</tr>
<tr>
<td>Karlsson et al,§ 1995</td>
<td>1129 (100)</td>
<td>351 (31)</td>
<td>385 (34)</td>
<td>114 (10)</td>
<td>4, 5, 6, 7</td>
</tr>
<tr>
<td>Kug and Leitner,§ 1989</td>
<td>179 (100)</td>
<td>11 (6)</td>
<td>21 (12)</td>
<td>8 (4)</td>
<td>5, 10</td>
</tr>
<tr>
<td>Malano and Pejicivanov,§ 1995</td>
<td>118 (100)</td>
<td>0</td>
<td>81 (69)</td>
<td>57 (48)</td>
<td>5, 6, 7, 8</td>
</tr>
<tr>
<td>Mascarelli et al,§ 1993</td>
<td>25 (100)</td>
<td>NS</td>
<td>6 (24)</td>
<td>3 (12)</td>
<td>4</td>
</tr>
<tr>
<td>Nasri and Coast,§ 1989</td>
<td>90 (100)</td>
<td>3 (3)</td>
<td>25 (28)</td>
<td>6 (7)</td>
<td>5, 6</td>
</tr>
<tr>
<td>Nasri et al,§ 1991</td>
<td>59 (100)</td>
<td>0</td>
<td>22 (37)</td>
<td>7 (12)</td>
<td>5, 6</td>
</tr>
<tr>
<td>Osmers et al,§ 1990</td>
<td>98 (100)</td>
<td>0</td>
<td>65 (66)</td>
<td>13 (13)</td>
<td>6</td>
</tr>
<tr>
<td>Osmers et al,§ 1992</td>
<td>233 (100)</td>
<td>NS</td>
<td>158 (68)</td>
<td>27 (12)</td>
<td>6</td>
</tr>
<tr>
<td>Peril et al,§ 1996</td>
<td>150 (100)</td>
<td>35 (23)</td>
<td>67 (45)</td>
<td>19 (13)</td>
<td>5, 10</td>
</tr>
<tr>
<td>Schramm et al,§ 1995</td>
<td>195 (100)</td>
<td>0</td>
<td>107 (55)</td>
<td>29 (15)</td>
<td>4</td>
</tr>
<tr>
<td>Seelbich-Gobel et al,§ 1995</td>
<td>232 (100)</td>
<td>NS</td>
<td>100 (43)</td>
<td>39 (17)</td>
<td>6, 8</td>
</tr>
<tr>
<td>Smith et al,§ 1991</td>
<td>45 (100)</td>
<td>12 (27)</td>
<td>9 (20)</td>
<td>4 (9)</td>
<td>6</td>
</tr>
<tr>
<td>Taviani et al,§ 1995</td>
<td>41 (100)</td>
<td>NS</td>
<td>16 (39)</td>
<td>2 (5)</td>
<td>5</td>
</tr>
<tr>
<td>Van den Bosch et al,§ 1995</td>
<td>126 (100)</td>
<td>0</td>
<td>56 (44)</td>
<td>6 (5)</td>
<td>4</td>
</tr>
<tr>
<td>Vaner et al,§ 1991</td>
<td>15 (100)</td>
<td>9 (60)</td>
<td>6 (40)</td>
<td>2 (13)</td>
<td>4, 5, 6</td>
</tr>
<tr>
<td>Volger et al,§ 1996</td>
<td>380 (44)</td>
<td>NS</td>
<td>174 (46)</td>
<td>41 (11)</td>
<td>6</td>
</tr>
<tr>
<td>Weigel et al,§ 1990</td>
<td>101 (58)</td>
<td>NS</td>
<td>48 (48)</td>
<td>15 (15)</td>
<td>3, 6, 8</td>
</tr>
<tr>
<td>Weigel et al,§ 1995</td>
<td>200 (50)</td>
<td>0</td>
<td>112 (56)</td>
<td>37 (19)</td>
<td>4, 5, 6, 7</td>
</tr>
<tr>
<td>Wolman et al,§ 1996</td>
<td>54 (100)</td>
<td>0</td>
<td>18 (33)</td>
<td>4 (7)</td>
<td>4, 5, 6, 7</td>
</tr>
<tr>
<td>Zannoni et al,§ 1994</td>
<td>761 (100)</td>
<td>0</td>
<td>181 (24)</td>
<td>56 (7)</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>5892 (94)</td>
<td>2368 (40)</td>
<td>759 (13)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*NS indicates not stated.
†Includes cancer, atypical and complex hyperplasia, and polyps in this definition of endometrial disease.
‡Thickness threshold used to define an abnormal test result.
§Non–English-language studies.

We included many studies on the basis of methodologic criteria. A sensitivity analysis was performed to determine if including these studies would have had a significant impact on the overall results. All studies that were excluded were included in the sensitivity analysis if data could be extracted (n = 8), except studies that evaluated EVUS in asymptomatic women as a screening test for cancer and studies that evaluated EVUS in women receiving tamoxifen.

RESULTS

A total of 35 studies (14 non–English language) including 5892 women met inclusion criteria (Table 1). The mean age of the women was 61 years, and 94% were symptomatic with vaginal bleeding. The prevalence of endometrial cancer was 13% and of endometrial polyps or hyperplasia 40%. Within the studies that included women using hormone replacement therapy, 471 (26%) of the 1781 women were currently using such therapy. Sixteen studies reported the number of women who could not tolerate EVUS (mean, 0; SD, 2%) and 14 studies reported the number of women who had a nondiagnostic EVUS result (mean, 0; SD, 2%).

The mean (SD) endometrial thickness was 4 (1) mm for women with normal histological findings, 10 (3) mm for women with endometrial polyps, 14 (4) mm for women with hyperplasia, and 20 (6) mm for women with cancer.

Sensitivity

Endovaginal ultrasound was better at detecting cancer than it was at detecting polyps or hyperplasia (Table 2). For example, using a 5-mm threshold, 96% (95% CI, 94%–98%) of women with cancer had an abnormal EVUS result, whereas 92% (95% CI, 90%–93%) of women with endometrial disease had an abnormal EVUS result. Endovaginal ultrasound was equally accurate at identifying women with endometrial disease regardless of whether they were using hormone replacement therapy (Table 3). For example, at a 5-mm thickness, EVUS identified 95% (95% CI, 93%–97%) of endometrial disease among women not using hormone replacement therapy, and 91% (95% CI, 89%–93%) of endometrial disease among women who were using hormone replacement therapy.

Specificity

In general, specificity was higher for endometrial disease than cancer (Table 2). For all endometrial thickness thresh-
Stratifying by hormone replacement therapy (Figure 2, A) but retained among women who used hormone replacement therapy (Figure 2, B). Heterogeneity improved among women who were not using hormone replacement therapy (Table 2, A) but remained among women who used hormone replacement therapy (Figure 2, B). Stratifying by other factors, including whether studies were English language or non–English language, patient symptoms, specialty of the examiner, whether fluid was included or excluded from the endometrial thickness measurement, whether a single or double wall measurement was used, and whether "or" or "and" was used as the upper limit of normal did not improve consistency across studies.

Summary ROC Curves

Changing the threshold of endometrial thickness used to define an abnormal EVUS result in the expected trade-off between sensitivity and specificity. (There was no trade-off within the individual thickness thresholds.) By increasing the thickness used to define an abnormal EVUS result, more abnormalities were missed, but there were fewer false-positives (Table 2, A). For example, at a 3-mm cutoff, the test detected 98% of women with endometrial disease, but identified 38% of women with normal histological findings as abnormal. At a 10-mm thickness the test detected fewer women with disease (66%) and identified fewer women with abnormal histological findings as abnormal (12%). In general, EVUS was more accurate in women who were not using hormone replacement therapy (Table 3).

The summary ROCs that combine data from all of the thickness thresholds were significantly different between women who were using hormone replacement therapy and women who were not (P = .02; Figure 3), and there was greater accuracy among women who were not using hormone replacement therapy. The summary ROCs were not significantly different among women who were using hormone replacement therapy and women in whom hormone replacement therapy use was not stated (P = .36).

Positive and Negative Likelihood Ratios and the Risk of Abnormality

Because the sensitivity of EVUS did not vary significantly with hormone use, EVUS is equally accurate in excluding endometrial disease regardless of hormone use. For example, at a 5-mm threshold, the negative likelihood ratio was 0.05 for women who did not use hormone replacement therapy and 0.12 for women who did use hormone replacement therapy (Table 3).
women who used hormone replacement (Table 8). Thus, a woman with a 10% pretest probability of endometrial disease has a 1% risk of disease following a normal EVUS result (Table 4). Because specificity of EVUS varied with hormone use, the ability of EVUS to predict endometrial disease varies by hormone therapy use. At a 5-mm threshold, the positive likelihood ratio was 11.9 among women who did not use hormone replacement but only 4.0 among women who used hormone replacement (Table 3). Thus, a woman with a 10% pretest probability of any endometrial disease has a 57% risk of disease following an abnormal EVUS result if she is not using hormone replacement therapy but only a 31% risk of disease if she is using hormone replacement therapy (Table 4). The risk of having endometrial disease following a normal and abnormal EVUS result is shown for a range of pretest probabilities (Table 4).

**Sensitivity Analysis**

Inclusion of results from excluded studies had little impact. For example, at a threshold of 5 mm, the sensitivity for cancer alone was 96% among the included studies (n = 457) and was 95% among the excluded studies (n = 75). Similarly at 5 mm, the specificity for cancer alone decreased from 92% to 88%, and the sensitivity for cancer alone decreased from 96% to 95%.

**COMMENT**

We found that EVUS is a sensitive test for detecting endometrial disease. Using a thickness of 5 mm, the sensitivity for detecting any endometrial disease was 92%, and the sensitivity for detecting cancer was 96%. These estimates did not vary by use of hormone replacement therapy. The high sensitivity of EVUS makes it an excellent noninvasive test for determining which women with vaginal bleeding do not require endometrial biopsy. The specificity is low, and thus ultrasound is not very accurate in predicting endometrial disease. Therefore, an abnormal EVUS result in a woman with vaginal bleeding needs to be followed by a histological biopsy.

Like all techniques, EVUS imaging will fail to detect cancer and other abnormalities in some women. However, a false-negative rate of 8% must be compared with endometrial biopsy techniques. Office-based endometrial biopsy devices, the most commonly used means to sample the endometrium, have false-negative rates of 5% to 15%, and dilation and curettage, an invasive procedure, has false-negative rates of 2% to 6%. It is not surprising that EVUS misses fewer abnormalities than office-based endometrial biopsy because ultrasound imaging allows visualization of the entire endometrial cavity, whereas most biopsy techniques rely on blind sampling. This meta-analysis suggests that the sensitivity of EVUS is at least as good as office-based endometrial biopsy techniques.

There are several benefits of EVUS compared with endometrial biopsy. Endovaginal ultrasound is less invasive, well tolerated, generally painless, without complications, and nondiagnostic in a small percentage of cases. Some women cannot undergo successful office endometrial biopsy secondary to cervical stenosis because of a small introitus, pain, or intolerance of the procedure. An invasive dilatation and curettage is then required to obtain a diagnosis. Postmenopausal women with vaginal bleeding often undergo multiple biopsies, because insufficient tissue is obtained for diagnosis or because of recurrent bleeding. A negative EVUS could reduce the need to undergo multiple biopsies. Endovaginal ultrasound is well suited to evaluate persistent bleeding despite a histological diagnosis of atrophy. A thin endovaginal thickness measurement supports the diagnosis of atrophy, whereas a thickened measurement would suggest that there was inadequate sampling of the endometrium and that a pathologic diagnosis may have been missed. Lastly, the cost of EVUS has compared favorably with endometrial biopsy in the evaluation of postmenopausal bleeding.

Ultrasound cannot discriminate between proliferative endometrium, benign endometrial disease, and cancer; all of which cause an increase in endometrial thickness. Because postmenopausal

---

**Figure 1.**—Sensitivity (A) and specificity (B) for endometrial disease using a 5-mm endometrial thickness. CI indicates confidence interval. The vertical line represents the summary estimate (95% CI).
hormone replacement therapy may cause proliferation of the endometrium, EVUS is less specific in women using hormone replacement therapy. The fact that different regimens of estrogen and progestins affect the endometrium differently may account for the variability in reported specificity of EVUS in women using hormone replacement therapy. Additionally, the different rates of reported hormone replacement therapy use may have contributed to the variability in reported specificity. It is possible that if 100% of the women were using hormone replacement therapy that the specificity would be substantially less than we report.

Fewer than half of the studies reported the rate of nondiagnostic EVUS examinations. A nondiagnostic test may occur more often in women with invasive carcinoma in whom the endometrial cavity can be difficult to visualize. In cases where the endometrium is incompletely visualized, it is important for the examination to be interpreted as nondiagnostic. In these cases, dilation and curettage, hysteroscopy, sonohysterography, or magnetic resonance imaging can be performed to further evaluate the endometrium.

Positive and negative likelihood ratios can be used to estimate a patient’s posttest probability of disease. The positive likelihood ratio is used to calculate the probability of disease after a positive test result (rule in disease), whereas the negative likelihood ratio is used to calculate the probability of disease after a negative test result (rule out disease). At a 5-mm-thickness cutoff, the negative likelihood ratios were approximately 0.1 regardless of hormone use. Thus, a negative EVUS result can decrease a pretest odds of cancer by approximately 90% in women regardless of hormone use. A woman with a 1% risk of cancer, which is the risk associated with vaginal bleeding in a postmenopausal woman who is not using hormone replacement therapy, will have a 1% probability of cancer following a negative ultrasound examination result.

Tests of homogeneity are important in evaluating the appropriateness of combining the results of different studies. We found that the sensitivity of EVUS was high, independent of hormone replacement therapy, and consistent across studies. One study contributed the majority of the heterogeneity noted for the estimate of sensitivity.79 The low sensitivity for detecting endometrial disease using the 4-mm cutoff (Tables 2 and 3) is a reflection of this study. If this study was excluded, the results changed only slightly.

We excluded studies that evaluated the endometrium in women taking tamoxifen, which causes marked thickening of the endometrium and increases the risk of en-

![Figure 2](https://example.com/figure2.png)

**Figure 2.**—Specificity for endometrial disease (A, without hormone replacement therapy; B, with hormone replacement therapy) using a 5-mm endometrial thickness cutoff. CI indicates confidence interval. The vertical line represents the summary estimate (95% CI).

![Figure 3](https://example.com/figure3.png)

**Figure 3.**—Summary receiver operating curves stratified by hormone replacement therapy use.

![Table 4](https://example.com/table4.png)

**Table 4.**—Risk of a Woman Having Endometrial Disease Following an Endovaginal Ultrasound (EVUS) Using a Cutoff of 5 mm to Define an Abnormal Test Result, Stratified by Hormone Replacement Therapy (HRT) Use and Pretest Probability of Disease*.
dometial abnormality.41,112 We did not include the results of studies that focused on the use of EVUS as a screening test for cancer in asymptomatic women because endometrial cancer is rare, most women with endometrial cancer have vaginal bleeding, and the false positives would outnumber the true positives in an asymptomatic population.56

While we included 2 unpublished studies, we may have missed other unpublished work with negative results, whose inclusion may have lowered overall test accuracy. However, it is unlikely that we missed any large studies, and smaller studies are unlikely to substantially affect the results. Additionally, the results may reflect the accuracy of specialized centers that have published data, and this may inflate the accuracy available in a general community setting.

In summary, we found that a thin (<5-mm) endometrial measurement on EVUS can exclude endometrial disease in the majority of postmenopausal women with vaginal bleeding, regardless of hormone replacement use. Endovaginal ultrasound has similar sensitivity as endometrial biopsy and can be used when endometrial biopsy is not available, non-diagnostic, or unsuccessful.

We thank Warren Browner, MD, and Andrew Bindman, MD, for their review of the manuscript and Loreto Carmona, MD, for her helpful review of studies included in the meta-analysis.

References


©1998 American Medical Association. All rights reserved.


90. Weigel M, Krisse K, Strittmatter HJ, Melchert F. Measuring the thickness—is that all we have to do for sonographic assessment of endometrium in postmenopausal women? Ultrasound Obstet Gynecol. 1996;6:162-164.

