Review

Endovaginal Ultrasound to Exclude Endometrial Cancer and Other Endometrial Abnormalities

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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.

Data Sources.—Literature search of English-language and non–English-language articles published from 1966 through November 1996 using MEDLINE and by a manual search of bibliographies of published articles.

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.

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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,[4,6,7] 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.[3,11,13-96] 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-

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metrial measurement.[17,38,79] 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*, *dilatation 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, dilatation and curettage, or hysterectomy) were included. Retrospective studies,[19,33,34,62,72,77] studies with selective histological sampling,[23,24,29,39,52,62,69] studies that reported results pooled for premenopausal and postmenopausal women,[42,71,84,97] and studies that measured endometrial thickness following tissue sampling[13,17,23,42,49,58,62] were excluded. In addition, studies that evaluated EVUS only in asymptomatic women,[16,35,67,69,81,93,98,99] women receiving tamoxifen,[31,32,51,56,59,75] and women with known endometrial cancer[43,58,100,101]; studies not reporting endovaginal thickness measurements[15,26,52,71,72,74,76,77]; and studies where the crude data could not be extracted[19,21,24,39,42,48,52,72,81,85,97] 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.[20,61] For studies that resulted in multiple publications, data from the most recent publication were used.[34,69]

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 polyps), and normal (atrophy, normal). Endometrial disease was defined as including cancer and benign endometrial abnormalities. Within each study, cases of cervical cancer 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,[16,53,54,63,70,80,83,90] 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 3% to 60%.

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.[102] 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: $\Sigma[(\text{sensitivity}_i)(n_i)]/(n_1 + n_2 + \ldots\ n_i)$. 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.[103] Possible reasons for heterogeneity, such as whether the study was published in the English languge 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[104] 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

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Table 1.—Prospective Studies Comparing Endovaginal Ultrasound Measurements With Endometrial Histology in Postmenopausal Women Included in Meta-analysis

Source, y	No. (%)				Endometrial Thickness Cutoffs, mm‡
	Vaginal Bleeding	Hormone Replacement Therapy*	Endometrial Disease†	Cancer	
Abu Hmeidan et al,[16] 1992§	545 (100)	NS	274 (50)	86 (16)	5
Aleem et al,[18] 1995	42 (33)	0	23 (55)	14 (33)	8
Auslender et al,[20] 1993	134 (100)	0	66 (49)	16 (12)	3, 4, 5, 6, 7, 8, 10
Botsis et al,[22] 1992	120 (100)	0	22 (18)	8 (7)	5, 10
Brolmann et al,[27] 1993§	54 (100)	0	32 (59)	10 (19)	6, 8
Cacciatore et al,[28] 1994	45 (100)	20 (44)	23 (51)	4 (9)	5
Chan et al,[30] 1994	67 (100)	0	29 (43)	17 (25)	4, 5, 6, 7
Degenhardt et al,[36] 1991§	37 (100)	NS	37 (27)‖	37 (100)	6
Dijkhuizen et al,[37] 1996	69 (100)	0	31 (45)	8 (12)	6, 8, 10
Dorum et al,[38] 1993	100 (100)	12 (12)	25 (25)	15 (15)	5
Goldstein et al,[44] 1990	28 (100)	18 (64)	6 (21)	1 (4)	5
Granberg et al,[45] 1991	175 (100)	0	48 (27)	18 (10)	5
Hanggi et al,[50] 1995§	89 (100)	0	25 (28)	21 (24)	5
Karlsson et al,[53] 1993	105 (100)	NS	35 (33)	15 (14)	5
Karlsson et al,[54] 1994	51 (100)	NS	35 (69)	0 (0)	4
Karlsson et al,[55] 1995	1129 (100)	351 (31)	385 (34)	114 (10)	4, 5, 6, 7
Klug and Leitner,[57] 1989§	179 (100)	11 (6)	21 (12)	8 (4)	5, 10
Malinova and Pehlivanov,[61] 1995	118 (100)	0	81 (69)	57 (48)	5, 6, 7, 8
Mascaretti et al,[63] 1993§	25 (100)	NS	6 (24)	3 (12)	4
Nasri and Coast,[64] 1989	90 (100)	3 (3)	25 (28)	6 (7)	5, 6
Nasri et al,[65] 1991	59 (100)	0	22 (37)	7 (12)	5, 6
Osmers et al,[68] 1990	98 (100)	0	65 (66)	13 (13)	6
Osmers et al,[70] 1992§	233 (100)	NS	158 (68)	27 (12)	6
Pertl et al,[73] 1996§	150 (100)	35 (23)	67 (45)	19 (13)	5, 10
Schramm et al,[79] 1995§	195 (100)	0	107 (55)	29 (15)	4
Seelbach-Gobel et al,[80] 1995§	232 (100)	NS	100 (43)	39 (17)	6, 8
Smith et al,[82] 1991	45 (100)	12 (27)	9 (20)	4 (9)	6
Taviani et al,[83] 1995§	41 (100)	NS	16 (39)	2 (5)	5
Van den Bosch et al,[87] 1995	126 (100)	0	56 (44)	6 (5)	4
Varner et al,[88] 1991	15 (100)	9 (60)	6 (40)	2 (13)	4, 5, 6
Volgger et al,[89] 1996§	380 (44)	NS	174 (46)	41 (11)	6
Weigel et al,[90] 1990§	101 (58)	NS	48 (48)	15 (15)	3, 6, 8
Weigel et al,[91] 1995	200 (50)	0	112 (56)	37 (19)	4, 5, 6, 7
Wolman et al,[92] 1996	54 (100)	0	18 (33)	4 (7)	4, 5, 6, 7
Zannoni et al,[95] 1994§	761 (100)	0	181 (24)	56 (7)	4
Total	**5892 (94)**		**2368 (40)**	**759 (13)**	

*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.
‖Overall, 137 patients were included in this study (prevalence of cancer, 37/137), although only the results for cancer were abstracted and included in Table 2. These patients were not included in the calculations of any endometrial disease.

used hormone replacement therapy and women in whom hormone replacement therapy use was not stated.

We excluded 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-

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Table 2.—Summary Sensitivity and Specificity for Endometrial Disease and Cancer Using Different Endovaginal Thickness Measurements to Define an Abnormal Result*

	Endometrial Disease†				Cancer			
Threshold, mm‡	No. of Women§	Sensitivity (95% CI), %	No. of Women§	Specificity (95% CI), %	No. of Women§	Sensitivity (95% CI), %	No. of Women§	Specificity (95% CI), %
3	114	98 (94-100)	121	62 (53-71)	31	100 (89-100)	204	38 (32-45)
4‖	1001	91 (89-93)	1756	69 (67-71)	284	96 (93-98)	2422	53 (51-55)
5	1306	92 (90-93)	2137	81 (79-83)	457	96 (94-98)	2986	61 (59-63)
6¶	1361	87 (85-89)	1717	82 (80-84)	454	95 (92-97)	2661	55 (53-57)
7#	691	85 (82-88)	1011	90 (88-92)	131	95 (89-98)	442	64 (59-69)
8**	381	85 (81-88)	369	80 (75-84)	151	97 (92-99)	530	60 (56-64)
10**	207	66 (59-73)	445	88 (85-91)	51	90 (79-97)	532	79 (75-82)

*CI indicates confidence interval.
†Includes cancer, atypical and complex hyperplasia, and polyps in this definition of endometrial disease.
‡Thickness threshold used to define an abnormal test result.
§The number of women for whom data were available.
‖Results from Karlsson et al[54] are included only for endometrial disease.
¶Results from Dengenhardt et al[36] are not included for endometrial disease.
#Results from Karlsson et al[55] are not included for cancer.
**Results from Dijkhuizen et al[37] are not included for cancer.

Table 3.—Accuracy of Endovaginal Ultrasound for Detecting Endometrial Disease, Stratified by Hormone Replacement Therapy at Various Endometrial Thickness Thresholds*

Thickness, mm	Hormone Replacement Therapy	No. of Women†	Sensitivity (95% CI), %	No. of Women†	Specificity (95% CI), %	Positive Likelihood Ratio	Negative Likelihood Ratio
3	No	66	98 (92-100)	68	71 (58-81)	3.4	0.03
	Yes	48	98 (89-100)	53	51 (37-65)	2.0	0.04
4	No	569	86 (83-89)	968	70 (67-73)	2.9	0.20
	Yes	432	97 (95-98)	788	68 (65-71)	3.0	0.04
5	No	423	95 (93-97)	593	92 (90-94)	11.9	0.05
	Yes	883	91 (89-93)	1544	77 (75-79)	4.0	0.12
6	No	456	89 (86-92)	397	90 (87-93)	8.9	0.12
	Yes	905	86 (84-88)	1320	79 (77-81)	4.1	0.18
7	No	306	88 (84-91)	267	95 (92-97)	17.6	0.13
	Yes	385	83 (79-87)	744	88 (85-90)	6.9	0.19

*Endometrial disease includes cancer, atypical and complex hyperplasia, and polyps. CI indicates confidence interval.
†The number of women for whom data were available.

olds tested, specificity was better among women who did not use hormone replacement therapy (Table 3). For example, using a 5-mm thickness, among women with normal histological findings, 23% (95% CI, 21%-25%) of women using hormone replacement therapy had an abnormal EVUS result, whereas only 8% (95% CI, 6%-10%) of women who were not using hormone replacement therapy had an abnormal EVUS result.

Homogeneity

The estimates for sensitivity were highly consistent across studies. For example, for the outcome of cancer, using the 5-mm thickness, the studies were homogeneous. For the outcome of any endometrial disease, 2 of 20 studies were heterogeneous (Figure 1, A). In contrast, the specificity estimates were inconsistent across studies. For example, at a thickness threshold of 5 mm, 7 of the 20 articles were heterogeneous for the outcome of cancer, and 8 of the 20 articles were heterogeneous for the outcome of any endometrial disease (Figure 1, B). The estimates of specificity became less heterogeneous when the studies were stratified by use of hormone replacement therapy (Figure 2, A, and 2, B). Heterogeneity improved among women who were not using hormone replacement therapy (Figure 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 "≤" 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 examination resulted 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). 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 normal 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

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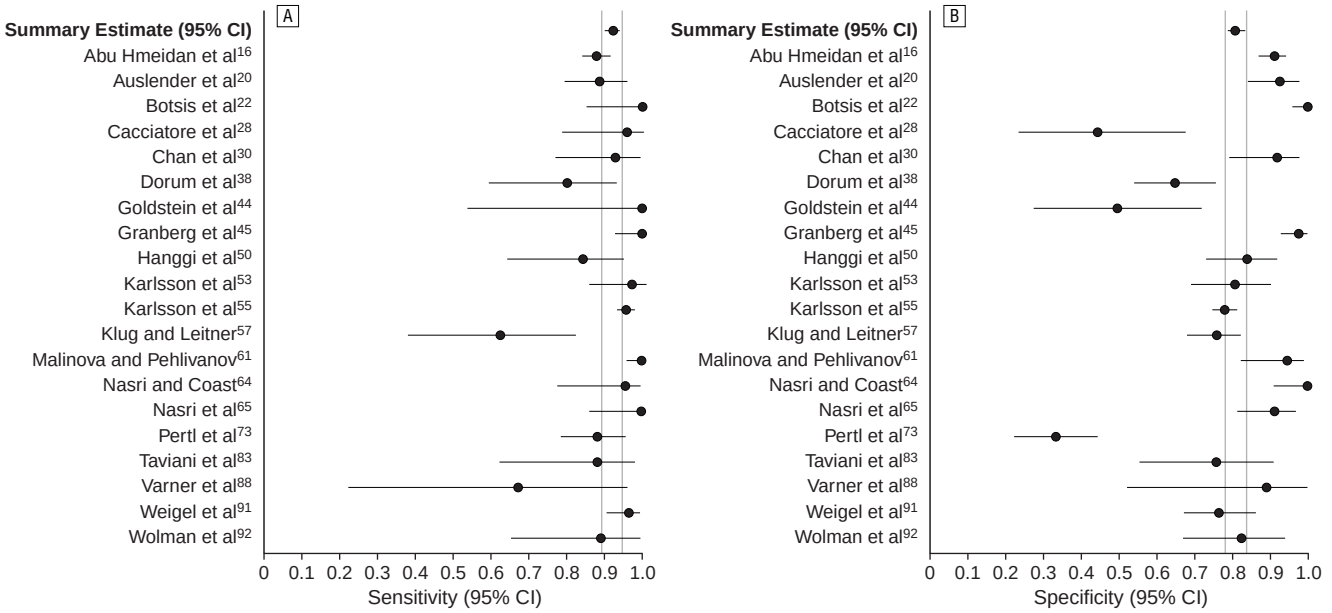

Figure 1.—Sensitivity (A) and specificity (B) for endometrial disease using a 5-mm endometrial thickness. CI indicates confidence interval. The vertical line represents the summary estimate (95% CI).

women who used hormone replacement (Table 3). 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 was 61% among the included studies (n = 2986) and was 59% among the excluded studies (n = 719). One study contributed approximately 25% of the patients to the pooled results.[55] When the findings of this article were eliminated, the results changed slightly; the sensitivity for endometrial disease 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%,[4-7,105-107] and dilation and curettage, an invasive procedure, has false-negative rates of 2% to 6%.[106,108-111] 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.[7,105,106,109-111] 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.[40] 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.[13,14] Lastly, the cost of EVUS has compared favorably with endometrial biopsy in the evaluation of postmenopausal bleeding.[12]

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

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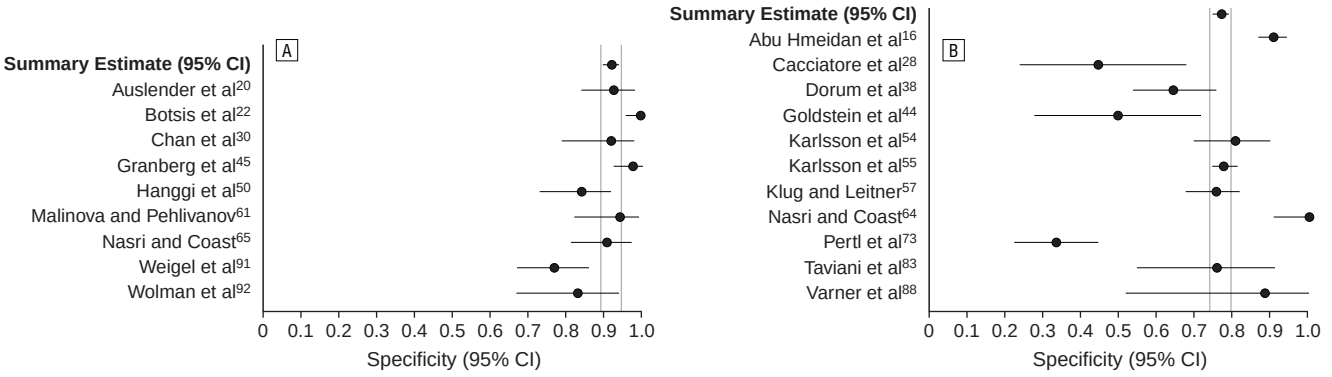

Figure 2.—Specificity for endometrial disease (A, without hormone replacement therapy; B, with horomone replacement therapy) using a 5-mm endometrial thickness. CI indicates confidence interval. The vertical line represents the summary estimate (95% CI).

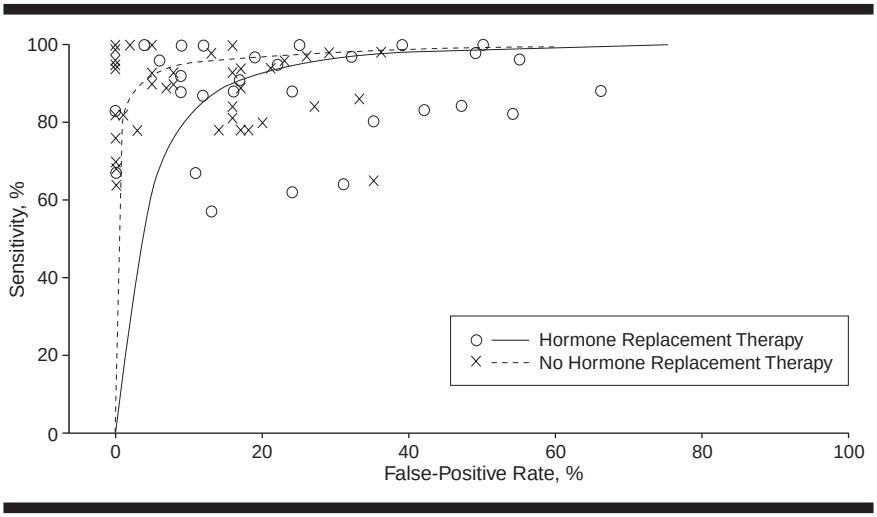

Figure 3.—Summary receiver operating curves stratified by hormone replacement therapy use.

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*

HRT	Pretest Probability, %	Posttest Probability of Endometrial Disease After an EVUS, %	
		Normal Result	Abnormal Result
No	1	0.1	11
Yes		0.1	4
No	5	0.3	39
Yes		0.6	17
No	10	0.6	57
Yes		1.3	31
No	20	1.3	75
Yes		2.9	50
No	50	5.1	92
Yes		11.0	80

*Includes cancer, atypical and complex hyperplasia, and polyps in this definition of endometrial disease.

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 using combined hormone replacement therapy, will have a 0.1% risk of cancer following a negative ultrasound examination result. A woman with a 10% pretest probability 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 sensitivity for endometrial disease improved from 92% to 94% using the 4-mm cutoff. One study contributed approximately 25% of the patients in our pooled results.[55] When 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-

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dometrial 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.[96]

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, nondiagnostic, or unsuccessful.

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References

1. Parker SL-TT, Bolden S, Wingo PA. Cancer statistics, 1996. *CA Cancer J Clin.* 1996;46:15-27.
2. Hawwa ZM, Nahhas WA, Copenhaver EH. Postmenopausal bleeding. *Lahey Clin Found Bull.* 1970; 19:61-70.
3. Rose PG. Endometrial carcinoma. *N Engl J Med.* 1996;335:640-649.
4. Einerth Y. Vacuum curettage by the Vabrar method: a simple procedure for endometrial diagnosis. *Acta Obstet Gynecol Scand.* 1982;61:373-376.
5. Lidor A, Ismajovich B, Confino E, David MP. Histopathological findings in 226 women with postmenopausal uterine bleeding. *Acta Obstet Gynecol Scand.* 1986;65:41-43.
6. Ferenczy A, Shore M, Guralnick M, Gelfand MM. The Kevorkian curette: an appraisal of its effectiveness in endometrial evaluation. *Obstet Gynecol.* 1979;54:262-267.
7. Stovall TG, Photopulos GJ, Poston WM, Ling FW, Sandles LG. Pipelle endometrial sampling in patients with known endometrial carcinoma. *Obstet Gynecol.* 1991;77:954-956.
8. Mestwerdt W, Kranzfelder D. Current diagnostic possibilities in endometrial carcinoma and its precursors. *Gynakologe.* 1983;16:87-92.
9. Ben BG, Seidman DS, Schiff E, Moran O, Menczer J. Outpatient endometrial sampling with the pipelle curette. *Gynecol Obstet Invest.* 1994;37:260-262.
10. Batool T, Reginald PW, Hughes JH. Outpatient pipelle endometrial biopsy in the investigation of postmenopausal bleeding. *Br J Obstet Gynaecol.* 1994;101:545-546.
11. Hunter RE, Reuter K, Kopin E. Use of ultrasonography in the difficult postmenopausal dilation and curettage. *Obstet Gynecol.* 1989;73:813-816.
12. Weber A, Belinson J, Bradley L, Piedmonte M. Vaginal ultrasonography versus endometrial biopsy in women with postmenopausal bleeding. *Am J Obstet Gynecol.* 1997;177:924-929.
13. Dubinsky TJ, Parvey HR, Gormaz G, Curtis M, Maklad N. Transvaginal hysterosonography: comparison with biopsy in the evaluation of postmenopausal bleeding. *J Ultrasound Med.* 1995;14:887-893.
14. Dubinsky TJ, Parvey HR, Gormaz G, Makland N. Transvaginal hysterosonography in the evaluation of small endoluminal masses. *J Ultrasound Med.* 1995;14:1-6.
15. Abu Hmeidan F, Baier D, Bilek K. Sonographic studies of patients with postmenopausal hemorrhage (endometrium/myometrium index). *Zentralbl Gynakol.* 1991;113:707-712.
16. Abu Hmeidan F, Bilek K, Baier D, Nuwayhid M, Kade R. Ultrasound image of endometrial cancer. *Ultraschall Med.* 1992;13:178-182.
17. Abu Hmeidan F, Bilek K, Baier D, Nuwayhid M, Kade R. Ultrasound assessment of the endometrium in early detection of endometrial cancer in high risk patients. *Zentralbl Gynakol.* 1992;114:455-458.
18. Aleem F, Predanic M, Calame R, Moukhtar M, Pennisi J. Transvaginal color and pulsed Doppler sonography of the endometrium: a possible role in reducing the number of dilatation and curettage procedures. *J Ultrasound Med.* 1995;14:139-145, 147-148.
19. Atri M, Nazarnia S, Aldis AE, Reinhold C, Bret PM, Kintzen G. Transvaginal US appearance of endometrial abnormalities. *Radiographics.* 1994;14: 483-492.
20. Auslender R, Bornstein J, Dirnfeld M, Kogan O, Atad J, Abramovich H. Vaginal ultrasound in patients with postmenopausal bleeding. *Ultrasound Obstet Gynecol.* 1993;3:426-428.
21. Bakos O, Smith P, Heimer G. Transvaginal ultrasonography for identifying endometrial pathology in postmenopausal women. *Maturitas.* 1994;20:181-189.
22. Botsis D, Kassanos D, Pyrgiotis E, Zourlas PA. Vaginal sonography of the endometrium in postmenopausal women. *Clin Exp Obstet Gynecol.* 1992; 19:189-192.
23. Bourne TH, Campbell S, Whitehead MI, Royston P, Steer CV, Collins WP. Detection of endometrial cancer in postmenopausal women by transvaginal ultrasonography and colour flow imaging. *BMJ.* 1990;301:369.
24. Bourne TH, Campbell S, Steer CV, Royston P, Whitehead MI, Collins WP. Detection of endometrial cancer by transvaginal ultrasonography with color flow imaging and blood flow analysis: a preliminary report. *Gynecol Oncol.* 1991;40:253-259.
25. Bourne TH. Evaluating the endometrium of postmenopausal women with transvaginal ultrasonography. *Ultrasound Obstet Gynecol.* 1995;6:75-80.
26. Brandner P, Gnirs J, Neis KJ, Hettenbach A, Schmidt W. Value of vaginal ultrasonography in noninvasive assessment of the endometrium of the postmenopausal uterus. *Geburtshilfe Frauenheilkd.* 1991;51:734-740.
27. Brolmann HA, van der Linden PJ, Bongers MY, Moret E, Meuwissen JH. Ultrasonographic diagnosis of endometrial disorders: correlation with the histological results in 112 patients. *Ned Tijdschr Geneeskd.* 1993;137:1823-1827.
28. Cacciatore B, Ramsay T, Lehtovirta P, Ylostalo P. Transvaginal sonography and hysteroscopy in postmenopausal bleeding. *Acta Obstet Gynecol Scand.* 1994;73:413-416.
29. Cecchini S, Ciatto S, Bonardi R, Grazzini G, Mazzota A. Endometrial ultrasonography: an alternative to invasive assessment in women with postmenopausal vaginal bleeding. *Tumori.* 1996;82:38-39.
30. Chan FY, Chau MT, Pun TC, et al. Limitations of transvaginal sonography and color Doppler imaging in the differentiation of endometrial carcinoma from benign lesions. *J Ultrasound Med.* 1994; 13:623-628.
31. Cohen I, Rosen DJ, Tepper R, et al. Ultrasonographic evaluation of the endometrium and correlation with endometrial sampling in postmenopausal patients treated with tamoxifen. *J Ultrasound Med.* 1993;12:275-280.
32. Cohen I, Rosen DJ, Shapira J, et al. Endometrial changes with tamoxifen: comparison between tamoxifen-treated and nontreated asymptomatic, postmenopausal breast cancer patients. *Gynecol Oncol.* 1994;52:185-190.
33. Conoscenti G, Meir Y, Fischer TL, et al. The diagnostic capacities of transvaginal echography and hysteroscopy in the characterization of endometrial pathology. *Minerva Ginecol.* 1995;47:293-300.
34. Conoscenti G, Meir YJ, Fischer TL, et al. Endometrial assessment by transvaginal sonography and histological findings after D & C in women with postmenopausal bleeding. *Ultrasound Obstet Gynecol.* 1995;6:108-115.
35. D'Amelio R, Perrone G, Di VF, et al. Echographic monitoring of the endometrium with a transvaginal probe in the menopause: a clinical study of 185 women in the menopause. *Minerva Ginecol.* 1994;46:551-556.
36. Degenhardt F, Bohmer S, Frisch K, Schneider J. Transvaginal ultrasonic assessment of the endometrium in menopause. *Ultraschall Med.* 1991;12: 119-123.
37. Dijkhuizen FP, Brolmann HA, Potters AE, Bongers MY, Heinz AP. The accuracy of transvaginal ultrasonography in the diagnosis of endometrial abnormalities. *Obstet Gynecol.* 1996;87:345-349.
38. Dorum A, Kristensen GB, Langebrekke A, Sornes T, Skaar O. Evaluation of endometrial thickness measured by endovaginal ultrasound in women with postmenopausal bleeding. *Acta Obstet Gynecol Scand.* 1993;72:116-119.
39. Emanuel MH, Verdel MJ, Wamsteker K, Lammes FB. A prospective comparison of transvaginal ultrasonography and diagnostic hysteroscopy in the evaluation of patients with abnormal uterine bleeding: clinical implications. *Am J Obstet Gynecol.* 1995;172:547-552.
40. Feldman S, Shapter A, Welch WR, Berkowitz RS. Two-year follow-up of 263 patients with post/perimenopausal vaginal bleeding and negative initial biopsy. *Gynecol Oncol.* 1994;55:56-59.
41. Fisher ER, Costantino J, Fisher B, Palekar AS, Redmond C, Mamounas E, for the National Surgical Adjuvant Breast and Bowel Project Collaborating Investigators. Pathologic findings from the National Surgical Adjuvant Breast Project (NSABP) Protocol B-17: intraductal carcinoma (ductal carcinoma in situ). *Cancer.* 1995;75:1310-1319.
42. Fleischer AC, Kalemeris GC, Machin JE, Entman SS, James AJ. Sonographic depiction of normal and abnormal endometrium with histopathologic correlation. *J Ultrasound Med.* 1986;5:445-452.
43. Georgiev DB, Chernev T, Netzov V, Dimova DN. Preoperative sonographic evaluation of patients with endometrial carcinoma. *Int J Gynaecol Obstet.* 1994;47:147-150.
44. 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;163:119-123.
45. Granberg S, Wikland M, Karlsson B, Norstrom A, Friberg LG. Endometrial thickness as measured by endovaginal ultrasonography for identifying endometrial abnormality. *Am J Obstet Gynecol.* 1991; 164:47-52.
46. Gredmark T, Kvint S, Havel G, Mattsson LA. Histopathological findings in women with postmenopausal bleeding. *Br J Obstet Gynaecol.* 1995; 102:133-136.
47. Grunfeld L, Walker B, Bergh PA, Sandler B, Hofmann G, Navot D. High-resolution endovaginal ultrasonography of the endometrium: a noninvasive test for endometrial adequacy. *Obstet Gynecol.* 1991; 78:200-204.
48. Gu CX, He FF, Xiang H. Differential diagnosis of endometrial abnormality by transvaginal sonography. *Chung Hua Fu Chan Ko Tsa Chih.* 1994;29: 720-723, 761.
49. Gupta JK, Wilson S, Desai P, Hau C. How should we investigate women with postmenopausal bleeding? *Acta Obstet Gynecol Scand.* 1996;75:475-479.
50. Hanggi W, Brandenberger AW, Ammann M, Laely A, Dietz TU, Herrmann U. Diagnosis of malignant uterine tumors by transvaginal ultrasound. *Ultraschall Med.* 1995;16:2-7.
51. Hulka CA, Hall DA. Endometrial abnormalities associated with tamoxifen therapy for breast can-

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cer: sonographic and pathologic correlation. *AJR Am J Roentgenol.* 1993;160:809-812.
52. Indman PD. Abnormal uterine bleeding: accuracy of vaginal probe ultrasound in predicting abnormal hysteroscopic findings. *J Reprod Med.* 1995; 40:545-548.
53. Karlsson B, Granberg S, Wikland M, Ryd W, Norstrom A. Endovaginal scanning of the endometrium compared to cytology and histology in women with postmenopausal bleeding. *Gynecol Oncol.* 1993; 50:173-178.
54. Karlsson B, Granberg S, Hellberg P, Wikland M. Comparative study of transvaginal sonography and hysteroscopy for the detection of pathologic endometrial lesions in women with postmenopausal bleeding. *J Ultrasound Med.* 1994;13:757-762.
55. 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: 1488-1494.
56. Kedar RP, Bourne TH, Powles TJ, et al. Effects of tamoxifen on uterus and ovaries of postmenopausal women in a randomised breast cancer prevention trial. *Lancet.* 1994;343:1318-1321.
57. Klug PW, Leitner G. Comparison of vaginal ultrasound and histologic findings of the endometrium. *Geburtshilfe Frauenheilkd.* 1989;49:797-802.
58. Kurjak A, Shalan H, Sosic A, et al. Endometrial carcinoma in postmenopausal women: evaluation by transvaginal color Doppler ultrasonography. *Am J Obstet Gynecol.* 1993;169:1597-1603.
59. Lahti E, Blanco G, Kauppila A, Apaja SM, Taskinen PJ, Laatikainen T. Endometrial changes in postmenopausal breast cancer patients receiving tamoxifen. *Obstet Gynecol.* 1993;81:660-664.
60. Maia HJ, Barbosa IC, Farias JP, Ladipo OA, Coutinho EM. Evaluation of the endometrial cavity during menopause. *Int J Gynaecol Obstet.* 1996;52: 61-66.
61. Malinova M, Pehlivanov B. Transvaginal sonography and endometrial thickness in patients with postmenopausal uterine bleeding. *Eur J Obstet Gynecol Reprod Biol.* 1995;58:161-165.
62. Malpani A, Singer J, Wolverson MK, Merenda G. Endometrial hyperplasia: value of endometrial thickness in ultrasonographic diagnosis and clinical significance. *J Clin Ultrasound.* 1990;18:173-177.
63. Mascaretti G, Carta G, Renzi E, Peluzzi C, Moscarini M. Evaluation of the endometrium by vaginal ultrasonography. *Minerva Ginecol.* 1993;45:1-4.
64. Nasri MN, Coast GJ. Correlation of ultrasound findings and endometrial histopathology in postmenopausal women. *Br J Obstet Gynaecol.* 1989;96: 1333-1338.
65. Nasri MN, Shepherd JH, Setchell ME, Lowe DG, Chard T. The role of vaginal scan in measurement of endometrial thickness in postmenopausal women. *Br J Obstet Gynaecol.* 1991;98:470-475.
66. Nasri MN, Shepherd JH, Setchell ME, Lowe DG, Chard T. Transvaginal ultrasound: a reliable basis for clinical management? case reports. *Br J Obstet Gynaecol.* 1991;98:485-486.
67. Osmers R, Volksen M, Rath W, Teichmann A, Kuhn W. Vaginosonographic measurement of the postmenopausal endometrium in the early detection of endometrial cancer. *Geburtshilfe Frauenheilkd.* 1989;49:262-265.
68. Osmers R, Volksen M, Schauer A. Vaginosonography for early detection of endometrial carcinoma? *Lancet.* 1990;335:1569-1571.
69. Osmers R, Volksen M, Rath W, Kuhn W. Vaginosonographic detection of endometrial cancer in postmenopausal women. *Int J Gynaecol Obstet.* 1990;32:35-37.
70. Osmers R, Volksen M, Kuhn W. Evaluation of the endometrium in postmenopausal women by means of vaginal ultrasound. *Rev Fr Gynecol Obstet.* 1992;87:309-315.
71. Pal A, Borthaiser Z. Experience with transvaginal ultrasonic examination in patients with metrorrhagia. *Orv Hetil.* 1994;135:1305-1307.
72. Persiani P, Perotti F, Riccardi A, Gallina D, Polatti F, Zara C. Diagnostic accuracy in transvaginal echography in benign endometrial diseases and its comparison with hysteroscopic biopsy. *Minerva Ginecol.* 1995;47:63-67.
73. Pertl B, Lahousen M, Pieber D, Heydarfadai HJ, Giuliani A. Value of ultrasound in early detection of endometrial carcinoma. *Gynakol Geburtshilfliche Rundsch.* 1996;36:14-20.
74. Possati G, Jasonni VM, Naldi S, et al. Ultrasound, hysteroscopy, and histological assessment of the endometrium in postmenopausal women. *Ann N Y Acad Sci.* 1994;734:479-481.
75. Rayter Z, Gazet JC, Shepherd J, et al. Gynaecological cytology and pelvic ultrasonography in patients with breast cancer taking tamoxifen compared with controls. *Eur J Surg Oncol.* 1994;20:134-140.
76. Rudelstorfer R, Nanz S, Bernaschek G. Vaginosonography and its diagnostic value in patients with postmenopausal bleeding. *Arch Gynecol Obstet.* 1990;248:37-44.
77. Salet-Lizee D, Gadonneix P, Van Den Akker M, Villet R. The reliability of study methods of the endometrium: a comparative study of 178 patients. *J Gynecol Obstet Biol Reprod (Paris).* 1993;22:593-599.
78. Schoenfeld A, Levavi H, Hirsch M, Pardo J, Ovadia J. Transvaginal sonography in postmenopausal women. *J Clin Ultrasound.* 1990;18:350-358.
79. Schramm T, Kurzl R, Schweighart C, Stuckert KA. Endometrial carcinoma and vaginal ultrasound: studies of the diagnostic validity. *Geburtshilfe Frauenheilkd.* 1995;55:65-72.
80. Seelbach-Gobel GB, Rempen A, Kristen P. Transvaginal ultrasound of the endometrium in postmenopause. *Geburtshilfe Frauenheilkd.* 1995; 55:59-64.
81. Shipley CR, Simmons CL, Nelson GH. Comparison of transvaginal sonography with endometrial biopsy in asymptomatic postmenopausal women. *J Ultrasound Med.* 1994;13:99-104.
82. Smith P, Bakos O, Heimer G, Ulmsten U. Transvaginal ultrasound for identifying endometrial abnormality. *Acta Obstet Gynecol Scand.* 1991;70:591-594.
83. Taviani A, Braccini S, Toniazzi P, et al. Transvaginal echography in patients with postmenopausal metrorrhagia. *Minerva Ginecol.* 1995;47:369-372.
84. Tongsong T, Pongnarisorn C, Mahanuphap P. Use of vaginosonographic measurements of endometrial thickness in the identification of abnormal endometrium in peri- and postmenopausal bleeding. *J Clin Ultrasound.* 1994;22:479-482.
85. Tsuda H, Kawabata M, Kawabata K, et al. Differences between Occidental and Oriental postmenopausal women in cutoff level of endometrial thickness for endometrial cancer screening by vaginal scan. *Am J Obstet Gynecol.* 1995;172:1494-1495.
86. Tsuda H, Kawabata M, Kawabata K, Yamamoto K, Hidaka A, Umesaki N. Comparison between transabdominal and transvaginal ultrasonography for identifying endometrial malignancies. *Gynecol Obstet Invest.* 1995;40:271-273.
87. Van den Bosch T, Vandendael A, Van Schoubroeck D, Wranz PA, Lombard CJ. Combining vaginal ultrasonography and office endometrial sampling in the diagnosis of endometrial disease in postmenopausal women. *Obstet Gynecol.* 1995;85:349-352.
88. Varner RE, Sparks JM, Cameron CD, Roberts LL, Soong SJ. Transvaginal sonography of the endometrium in postmenopausal women. *Obstet Gynecol.* 1991;78:195-199.
89. Volgger B, Alge A, Windbichler G, Zeimet AG, Muller HE, Marth C. Ultrasound morphologic evaluation of the postmenopausal endometrium: a prospective study. *Gynakol Geburtshilfliche Rundsch.* 1996;36:21-28.
90. Weigel M, Schmitt W, Lieder HJ, Inthraphuvasak J. The value of various parameters for ultrasound assessment of the postmenopausal endometrium with reference to benign and malignant neoplasms. *Geburtshilfe Frauenheilkd.* 1990;50:870-876.
91. Weigel M, Friese 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.* 1995;6:97-102.
92. Wolman I, Sagi J, Ginat S, Jaffa AJ, Hartoov J, Jedwab G. The sensitivity and specificity of vaginal sonography in detecting endometrial abnormalities in women with postmenopausal bleeding. *J Clin Ultrasound.* 1996;24:79-82.
93. Zacchi V, Zini R, Canino A. Transvaginal sonography as a screening method for the identification of patients at risk of postmenopausal endometrial pathology. *Minerva Ginecol.* 1993;45:339-342.
94. Zalud I, Conway C, Schulman H, Trinca D. Endometrial and myometrial thickness and uterine blood flow in postmenopausal women: the influence of hormonal replacement therapy and age. *J Ultrasound Med.* 1993;12:737-741.
95. Zannoni E, Radaelli U, Balestri M, Ferrazzi F. L'ecografia transvaginale nella valutazione dell'endometrio in pazienti con perdite ematiche atipiche in postmenopausa. In: D'Addario V, Cagnazzo G, eds. *ECO 1994.* Italy: CIC Edizioni Internazionali; 1994:27-30.
96. Langer RD, Pierce JJ, O'Hanlan KA, et al. Transvaginal ultrasonography compared with endometrial biopsy for the detection of endometrial disease: Postmenopausal Estrogen/Progestin Interventions Trial. *N Engl J Med.* 1997;337:1792-1798.
97. Promer H, Heiss O, Graf A, Batka M, Staudach A. Screening for endometrial cancer by Mi-Mark cytology and vaginal ultrasound. *Gynakol Geburtshilfliche Rundsch.* 1992;1:117-118.
98. Archer DF, McIntyre SK, Wilborn WJ, et al. Endometrial morphology in asymptomatic postmenopausal women. *Am J Obstet Gynecol.* 1991;165: 317-322.
99. Castelo BC, Puerto B, Duran M, et al. Transvaginal sonography of the endometrium in postmenopausal women: monitoring the effect of hormone replacement therapy. *Maturitas.* 1994;19:59-65.
100. Zorlu CG, Cobanoglu O, Ekici E, Ergun Y, Kuscu E, Gokmen O. Preoperative assessment of myometrial invasion of endometrial carcinoma by transvaginal ultrasonography. *Mater Med Pol.* 1995; 27:23-25.
101. Artner A, Bosze P, Gonda G. The value of ultrasound in preoperative assessment of the myometrial and cervical invasion in endometrial carcinoma. *Gynecol Oncol.* 1994;54:147-151.
102. Irwig L, Tosteson AN, Gatsonis C, et al. Guidelines for meta-analyses evaluating diagnostic tests. *Ann Intern Med.* 1994;120:667-676.
103. Aitchison J. Confidence-region tests. *J R Stat Soc.* 1964;3:462-476.
104. Moses LE, Shapiro D, Littenberg B. Combining independent studies of a diagnostic test into a summary ROC curve: data-analytic approaches and some additional considerations. *Stat Med.* 1993;12: 1293-1316.
105. Lipscomb GH, Lopatine SM, Stovall TG, Ling FW. A randomized comparison of the pipelle, accurette, and explora endometrial sampling devices. *Am J Obstet Gynecol.* 1994;170:591-594.
106. Stovall TG, Solomon SK, Ling FW. Endometrial sampling prior to hysterectomy [published erratum appears in *Obstet Gynecol.* 1989;74:105]. *Obstet Gynecol.* 1989;73:405-409.
107. Van den Bosch T, Vandendael A, Wranz PA, Lombard CJ. Endopap-versus pipelle-sampling in the diagnosis of postmenopausal endometrial disease. *Eur J Obstet Gynecol Reprod Biol.* 1996;64: 91-94.
108. Vuopala S. Diagnostic accuracy and clinical applicability of cytological and histological methods for investigating endometrial carcinoma. *Acta Obstet Gynecol Scand Suppl.* 1977;70:22-25.
109. Grimes DA. Diagnostic dilation and curettage: a reappraisal. *Am J Obstet Gynecol.* 1982;142:1-6.
110. Koonings P, Moyer D, Grimes D. A randomized clinical trial comparing pipelle and tis-u-trap for endometrial biopsy. *Obstet Gynecol.* 1990;75:293-295.
111. Stock R, Kanbour A. Prehysterectomy curettage. *Obstet Gynecol.* 1975;45:537-541.
112. Fornander T, Rutqvist LE, Cedermark B, et al. Adjuvant tamoxifen in early breast cancer: occurrence of new primary cancers. *Lancet.* 1989;1: 117-120.

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