TRANSVAGINAL ULTRASONOGRAPHY COMPARED WITH ENDOMETRIAL BIOPSY FOR THE DETECTION OF ENDOMETRIAL DISEASE

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ABSTRACT

Background Transvaginal ultrasonography is a noninvasive procedure that may be used to detect endometrial disease. However, its usefulness in screening for asymptomatic disease in postmenopausal women before or during treatment with estrogen or estrogen–progesterone replacement is not known.

Methods We compared the sensitivity and specificity of transvaginal ultrasonography and endometrial biopsy for the detection of endometrial disease in 448 postmenopausal women who received estrogen alone, cyclic or continuous estrogen–progesterone, or placebo for three years.

Results Concurrent ultrasonographic and biopsy results were available for 577 examinations in the 448 women, 99 percent of whom were undergoing routine annual follow-up. Endometrial thickness was less than 5 mm in 45 percent of the examinations, 5 to 10 mm in 41 percent, more than 10 mm in 12 percent, and not measured in 2 percent, and it was higher in the women receiving estrogen alone than in the other groups. Biopsy detected 11 cases of serious disease: 1 case of adenocarcinoma, 2 cases of atypical simple hyperplasia, and 8 cases of complex hyperplasia. Biopsy also detected simple hyperplasia in 20 cases. At a threshold value of 5 mm for endometrial thickness, transvaginal ultrasonography had a positive predictive value of 9 percent for detecting any abnormality, with 90 percent sensitivity, 48 percent specificity, and a negative predictive value of 99 percent. With this threshold, a biopsy would be indicated in more than half the women, only 4 percent of whom had serious disease.

Conclusions Transvaginal ultrasonography has a poor positive predictive value but a high negative predictive value for detecting serious endometrial disease in asymptomatic postmenopausal women. (N Engl J Med 1997;337:1792-8.)

ENDOMETRIAL biopsy is the standard test for detecting endometrial disease, but its value is limited by uncertainty about the origin of the tissue, which is obtained in a blind procedure, and the difficulty of obtaining adequate specimens in some women. Mainly on the basis of data from women presenting with uterine bleeding[1,2] or known disease,[3,4] transvaginal ultrasonography has been recommended as a less invasive substitute for biopsy in detecting endometrial disease.[5-11] Since the cost of these two procedures is similar, ultrasonography would be preferable if it were as useful in detecting endometrial disease as biopsy, because ultrasonography causes less discomfort and has fewer complications.

The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial provided an opportunity to compare ultrasonography with endometrial biopsy for the detection of endometrial hyperplasia in a largely asymptomatic cohort of postmenopausal women enrolled in a clinical trial of hormone-replacement therapy with estrogen or estrogen–progestin. In the PEPI trial, endometrial biopsy was performed at least annually; transvaginal ultrasonography was added during the second year. To determine the usefulness of ultrasonography in screening for endometrial disease in postmenopausal women, we studied the concordance of abnormal endometrial thickness, as measured by ultrasonography, with diagnoses based on histopathological examination of endometrial-biopsy specimens.

METHODS

The PEPI trial tested the effects of several ovarian-hormone–replacement regimens on risk factors for heart disease in postmenopausal women 45 to 64 years old who had been postmenopausal for no more than 10 years. Women with or without a uterus were randomly assigned to receive placebo or one of four active treatments for three years. All the active treatments included daily conjugated equine estrogens (0.625 mg per day). The treatments were estrogen alone, estrogen plus medroxyprogesterone acetate at a dose of 2.5 mg daily, estrogen plus medroxyprogesterone acetate at a dose of 10 mg per day for 12 days per month, and estrogen plus micronized progesterone at a dose of 200 mg per day for 12 days per month. The details of the study design and the primary results have been reported elsewhere.[12]

To be eligible for the study, women with a uterus had to have

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normal results on endometrial biopsy at base line. Endometrial biopsy was performed annually thereafter. Approximately halfway through the trial, these women were asked to undergo transvaginal ultrasonography before each biopsy. The original and modified protocols were approved by the institutional review board at each participating center, and all the women gave informed consent.

Endometrial Biopsy

Endometrial biopsies were performed at the time of the annual visits, regardless of whether the women had continued with their assigned treatment. Biopsies were not restricted to a particular time of the medication cycle. The day of the cycle was recorded. The biopsy results included in this analysis were obtained at the second or third annual visit. Additional biopsies were performed either as follow-up for abnormal biopsy results or if there was unexpected vaginal bleeding.

Histopathological Findings

All biopsy specimens were evaluated by at least two pathologists, one at the participating clinical center and another at the National Cancer Institute. When the two pathologists disagreed on the interpretation of the findings, a third pathologist served as arbiter. None of the pathologists were aware of the treatment assignments. When all three pathologists disagreed, the diagnosis was determined by the gynecologist at the participating center.[13] The diagnostic categories were normal, simple hyperplasia, complex hyperplasia, atypical hyperplasia, and adenocarcinoma. The last three categories were considered to represent seriously abnormal findings.

Ultrasonography

Transvaginal ultrasonography was performed no more than 48 hours before endometrial biopsy by technicians who were unaware of the treatment assignments. The uterus was scanned in the coronal and longitudinal projections with the use of 5.0-to-7.5-MHz vaginal transducers. The thickest anteroposterior diameter of the endometrial stripe was measured in the sagittal plane with either digital calipers on the display or manual calipers on an image recorded to scale. Alternatively, each layer of the endometrium was measured separately in the transverse plane of the longitudinal view, and the values were summed. The diameter of any fluid collection was subtracted. The hypoechoic halo sometimes seen surrounding the endometrial stripe was not included. The endometrial thickness was recorded in 1-mm increments.

A standard form was used to record the date of the examination, the equipment used, endometrial thickness, current hormone therapy, the technical adequacy of the examination, and in the case of a technically unsatisfactory examination, the contributing factors. A representative image was printed and affixed to the form.

Nearly all technically unsatisfactory ultrasonograms yielded thickness measurements. They were included in most of the analyses, because the primary goal of the study was to determine whether ultrasonography could replace biopsy. Some analyses, however, were stratified according to whether the ultrasonogram was satisfactory or unsatisfactory.

On the basis of reported data,[14-17] we selected 4 mm as the maximal normal endometrial thickness. Because some authors have used 8 mm[18] or 10 mm[19] as the upper limit for normal thickness, we also tested a threshold value of 9 mm in women receiving treatments associated with thicker endometria (estrogen alone and cyclical combinations). If the thickness could not be measured, the result was recorded as "no thickness."

Statistical Analysis

Means and standard deviations were calculated for demographic factors. Distributions of endometrial thickness were determined for each diagnostic category. Endometrial thicknesses of 5 mm or greater and 9 mm or greater were classified as abnormal for analyses of the sensitivity, specificity, and positive and negative predictive values of ultrasonography as compared with biopsy.

Because a goal of the study was to evaluate ultrasonography as a substitute for biopsy, the sensitivity and predictive values were recalculated after recoding unsatisfactory examinations with abnormal endometrial thickness from positive to negative, on the assumption that ultrasonographic screening would not be conclusive and biopsy would be needed. Similarly, sonograms yielding no thickness were excluded from the numerator in calculations of specificity, because, if no measurement was made, the absence of disease was not confirmed. Differences between women with satisfactory examinations and those with unsatisfactory examinations were evaluated by t-tests for continuous variables and Fisher's exact test for categorical factors. The association between the rate of unsatisfactory examinations and endometrial thickness was assessed with the use of a test for trends among proportions.[20] All statistical tests were two-sided. Cubic splines were used to fit smoothed receiver-operator-characteristic curves.[21]

RESULTS

The 875 women enrolled in the PEPI trial were similar to all U.S. women of the same age in terms of reproductive and gynecologic characteristics[22]; 596 of the women (68 percent) had a uterus. In this ancillary study, 458 women underwent 595 ultrasonographic examinations. The mean (±SD) age of the women was 59±4 years, the mean time since menopause was 8±3 years, and mean time since randomization was 31±5 months.

Biopsy results could not be matched with ultrasonographic results in 18 cases; the data from these examinations were excluded from the analyses. Thus, the present study describes the findings in 577 examinations performed in 448 women. Seven of these examinations (1 percent) were performed at a time other than an annual screening visit.

Forty ultrasonographic examinations were unsatisfactory. Of the 30 examinations for which a reason was given, uterine myoma was the reason in 25. The distribution of ultrasonographic examinations according to the availability of biopsy results, whether the examination was satisfactory, and treatment group is shown in Figure 1. Women with seriously abnormal histopathological findings were more likely to have unsatisfactory ultrasonographic examinations (27 percent vs. 7 percent, $P = 0.04$). An unsatisfactory ultrasonographic examination was associated with fewer pregnancies ($P = 0.03$) and a shorter time since menopause ($P = 0.05$) and was marginally associated with a higher body-mass index ($P = 0.07$) and no active hormone therapy ($P = 0.08$).

Twenty-six percent of the examinations were performed in women receiving placebo, 12 percent in women receiving estrogen therapy alone, 61 percent in women receiving estrogen–progestin therapy, and 2 percent in women receiving hormones prescribed by their physicians that were not part of the PEPI regimen and could not be categorized as unopposed estrogen, cyclical combined therapy, or continuous combined therapy.

The biopsy results were abnormal in 31 examina-

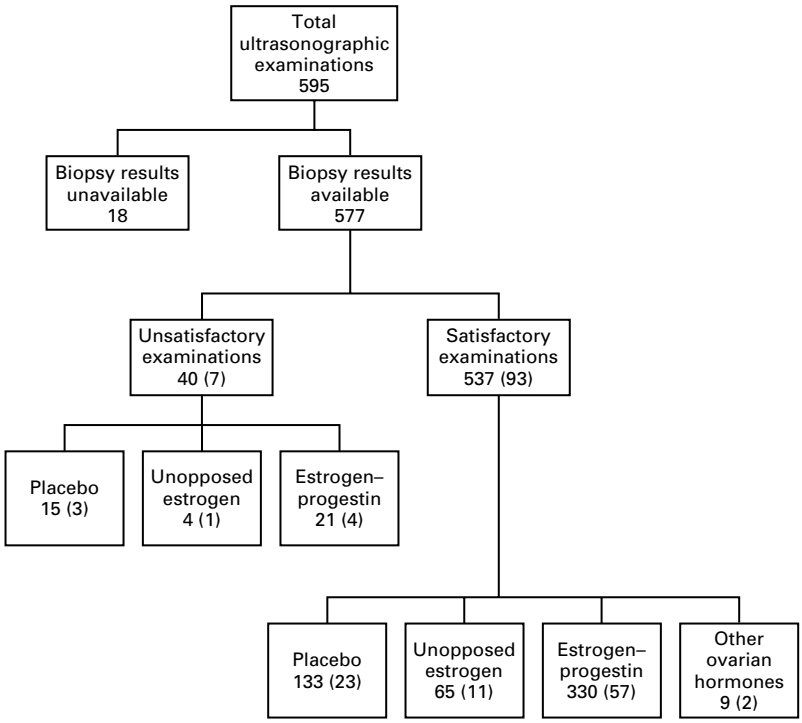

Figure 1. Transvaginal Ultrasonography and Treatment at the Time of Examination in Women Enrolled in the Postmenopausal Estrogen/Progestin Interventions Trial.

The numbers of examinations are shown, with percentages of examinations with both ultrasonographic and biopsy results available in parentheses.

tions (5 percent), and endometrial thickness was more than 4 mm in 307 examinations (53 percent). Table 1 shows the relation between the category of endometrial thickness and the histopathological diagnosis. The fraction of technically unsatisfactory ultrasonographic examinations increased slightly with increasing endometrial thickness (P for trend = 0.10). Table 2 shows the distributions of endometrial thickness and biopsy results according to the treatment assignment. The women receiving unopposed estrogen had the highest mean endometrial thickness and the highest rate of abnormal biopsy results; 34 percent of the biopsies in this group had abnormal results, as compared with 2 percent or less in each of the other groups.

Figure 2 shows endometrial thickness according to the histopathological diagnosis. Of the 31 biopsies with abnormal findings, 20 showed simple cystic hyperplasia and 11 showed serious abnormalities. The highest mean value for endometrial thickness was associated with complex hyperplasia (in eight cases); the values were lower in the two cases of atypical hyperplasia (7 and 12 mm) and the one case of adenocarcinoma (5 mm). Ultrasonography was unsatisfactory in three of the cases of serious abnormalities detected by biopsy.

Sensitivity, Specificity, and Positive and Negative Predictive Values

When all abnormal histopathological findings were considered, the 5-mm threshold for abnormal endometrial thickness had a sensitivity of 90 percent, a specificity of 48 percent, a positive predictive value of 9 percent, and a negative predictive value of 99 percent for detecting endometrial disease (Table 3). When only seriously abnormal histopathological findings were considered, the sensitivity was 91 percent, but the positive predictive value decreased to 3 percent. In an analysis that included all abnormal histopathological findings but excluded technically unsatisfactory ultrasonographic examinations (on the assumption that the evaluation was not complete after an unsatisfactory examination), the sensitivity of the 5-mm threshold for abnormal endometrial thickness decreased to 81 percent, the positive predictive value decreased to 8 percent, and the negative predictive value decreased to 95 percent. For seriously abnormal histopathological findings, the corresponding values were 73, 3, and 95 percent.

Twenty-three of the 31 biopsies with abnormal findings were in women receiving unopposed estrogen. When all abnormal histopathological findings were included in the analysis, the sensitivity and the

TABLE 1. ENDOMETRIAL THICKNESS AND BIOPSY FINDINGS IN POSTMENOPAUSAL WOMEN.

ENDOMETRIAL THICKNESS*	BIOPSY FINDING					
	NORMAL	SIMPLE HYPERPLASIA	COMPLEX HYPERPLASIA	ATYPICAL HYPERPLASIA	ADENO-CARCINOMA	TOTAL
	no. of examinations (no. of unsatisfactory examinations)					
<5 mm	259 (12)	2 (0)	0	0	0	261 (12)
5–10 mm	235 (14)	1 (0)	1 (0)	1 (1)	1 (0)	239 (15)
>10 mm	44 (5)	17 (1)	6 (0)	1 (1)	0	68 (7)
Thickness not recorded	8 (5)	0	1 (1)	0	0	9 (6)
Total examinations	546 (36)	20 (1)	8 (1)	2 (2)	1 (0)	577 (40)

*Endometrial thickness was determined by ultrasonography.

TABLE 2. MEAN ENDOMETRIAL THICKNESS AND DISTRIBUTION OF BIOPSY FINDINGS ACCORDING TO TREATMENT GROUP.*

TREATMENT GROUP	MEAN ENDOMETRIAL THICKNESS (RANGE)	BIOPSY FINDING					
		NORMAL	SIMPLE HYPERPLASIA	COMPLEX HYPERPLASIA	ATYPICAL HYPERPLASIA	ADENO-CARCINOMA	TOTAL
	mm	no. of examinations (%)					
Placebo	3.8 (1–15)	142 (98)	2 (1)	0	0	1 (1)	145
Estrogen alone	11.7 (1–26)	44 (66)	16 (24)	5 (7)†	2 (3)	0	67
Cyclic estrogen plus medroxyprogesterone acetate	6.4 (2–15)	121 (98)	1 (1)	2 (2)	0	0	124
Cyclic estrogen plus micronized progesterone	6.4 (1–14)	100 (99)	1 (1)	0	0	0	101
Continuous estrogen plus medroxyprogesterone acetate	4.5 (1–17)	122 (100)	0	0	0	0	122

*Percentages may not sum to 100 because of rounding. The analysis excludes nine examinations in which the thickness was not recorded and nine examinations in which treatment could not be classified.

†One case of complex hyperplasia in a woman receiving estrogen alone was excluded because the endometrial thickness was not recorded.

positive predictive value were higher in the women receiving unopposed estrogen (96 and 38 percent, respectively) than in the full cohort. This difference was largely due to the greater likelihood of simple hyperplasia in the group receiving unopposed estrogen. The specificity of ultrasonography for detecting disease in this group was much lower (10 percent). When simple hyperplasia was excluded, the positive predictive value for an endometrial thickness of 5 mm or more was also low (12 percent) in these high-risk women. When simple cystic hyperplasia was included but technically unsatisfactory examinations were excluded, the sensitivity was 83 percent, and the positive predictive value was 33 percent. These values fell to 63 and 8 percent, respectively, for seriously abnormal histopathological findings. There were only four ultrasonograms showing an endometrial thickness of less than 5 mm in the group of women taking unopposed estrogen, and since none of the four were associated with abnormal biopsy results, the negative predictive value was 100 percent.

The more liberal threshold for abnormal endometrial thickness (9 mm or more) was tested in women who received estrogen alone or cyclical estrogen plus progesterone. In the group of women receiving unopposed estrogen, an increase in the threshold from 5 to 9 mm resulted in an increase in the positive predictive value for detecting seriously abnormal histopathological findings, from 12 to 15 percent for all examinations and from 8 to 12 percent for satisfactory examinations. In women receiving combined cyclical treatment, the positive predictive value for an endometrial thickness of 9 mm or more was 2 percent for both categories of examinations.

Figure 3 shows the receiver-operator-characteristic

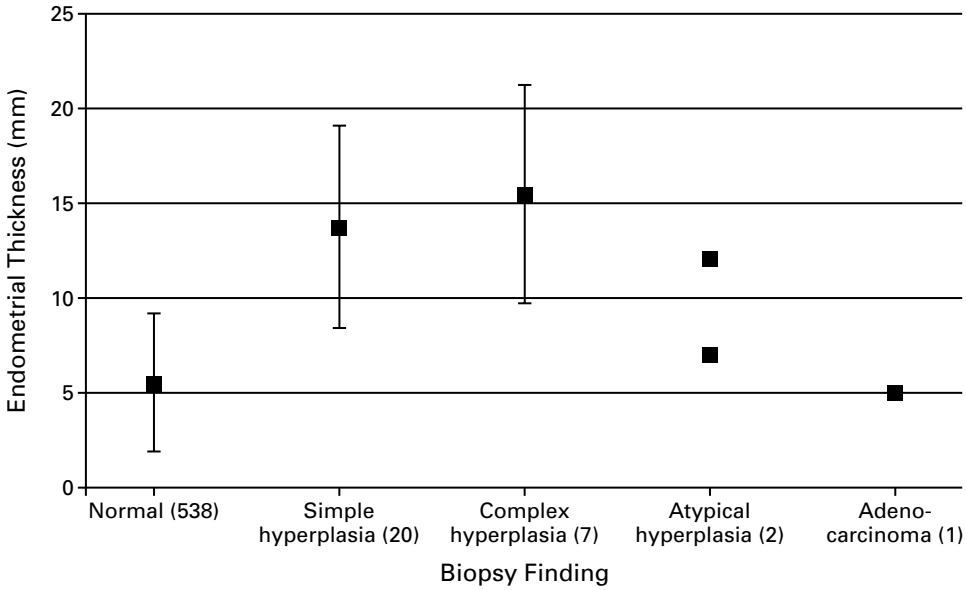

Figure 2. Mean (±SD) Endometrial Thickness According to Biopsy Findings.

Endometrial thickness was not recorded in one woman with complex hyperplasia. Numbers in parentheses are the numbers of examinations.

TABLE 3. SENSITIVITY, SPECIFICITY, AND POSITIVE AND NEGATIVE PREDICTIVE VALUES OF AN ENDOMETRIAL THICKNESS OF 5 mm OR MORE FOR DETECTING ENDOMETRIAL DISEASE.*

ENDOMETRIAL THICKNESS ≥5 mm	ANY ABNORMALITY	SERIOUS ABNORMALITY
	% (no. of examinations)†	
All ultrasonographic examinations		
Sensitivity	90 (28/31)	91 (10/11)
Specificity	48 (259/538)	—
Positive predictive value	9 (28/307)	3 (10/307)
Negative predictive value	99 (259/261)	100 (261/261)
Satisfactory ultrasonographic examinations		
Sensitivity	81 (25/31)	73 (8/11)
Specificity	46 (247/538)	—
Positive predictive value	8 (25/307)	3 (8/307)
Negative predictive value	95 (247/261)	95 (249/261)

*Serious abnormalities included complex hyperplasia, atypical hyperplasia, and adenocarcinoma. One ultrasonographic examination without a measurement of thickness in a woman with complex hyperplasia was included in the sensitivity and specificity calculations but excluded from the predictive-value calculations because it could not be classified as positive or negative.

†The numbers in parentheses are the numbers of examinations on which the calculations are based.

curves for any abnormal histopathological finding and for seriously abnormal findings in all women and in the women given estrogen alone.

DISCUSSION

This study was designed to compare transvaginal ultrasonography with endometrial biopsy as a screening procedure for endometrial disease in largely asymptomatic postmenopausal women receiving estrogen or estrogen–progesterone therapy. The inclusion of women receiving placebo provided the opportunity to compare these approaches in untreated women as well. We found that ultrasonography was useful for detecting endometrial hyperplasia. But hyperplasia was not synonymous with seriously abnormal histopathological findings, and the highest values for endometrial thickness were not associated with the most serious diagnoses. This disjunction was not attributable to the association between hyperplasia and unopposed-estrogen therapy, since the most serious disease, an adenocarcinoma, was in a woman in the placebo group. In another study of transvaginal ultrasonography, 300 asymptomatic postmenopausal women had no hyperplasia or cancer despite increased endometrial thickness, especially in heavier women.[23] The receiver-operator-characteristic curves in our study show that ultrasonography was better for detecting hyperplasia than serious abnormalities. As in other studies, for women receiving unopposed-estrogen therapy, the 9-mm threshold was superior to the 5-mm threshold. For the entire

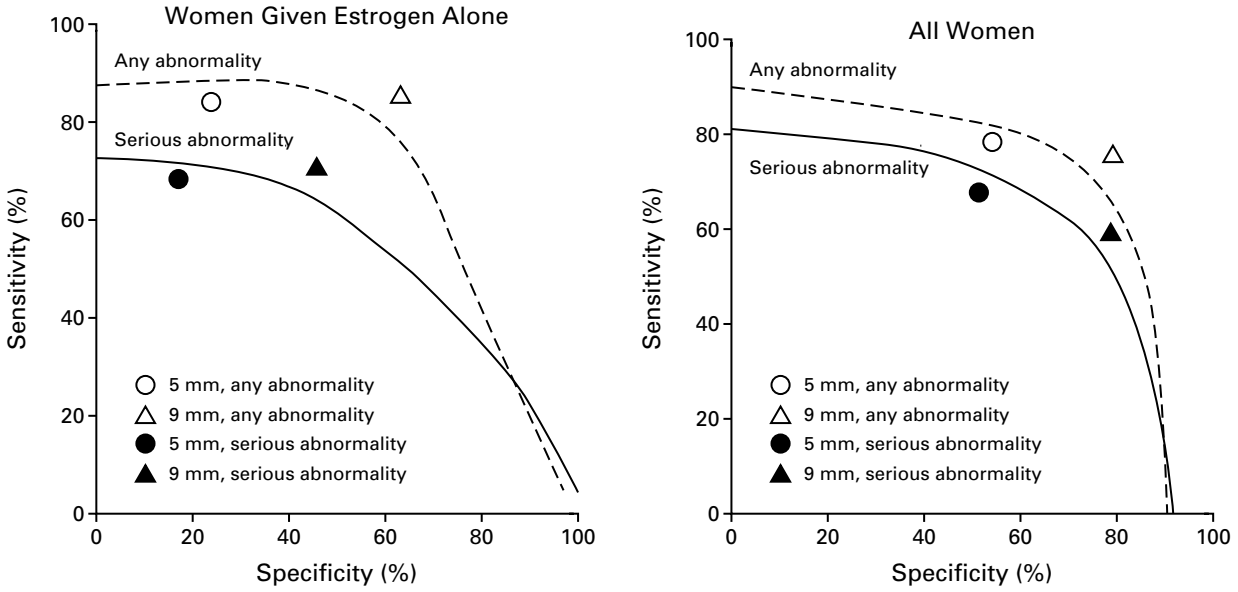

Figure 3. Receiver-Operator-Characteristic Curves for the Sensitivity and Specificity of Transvaginal Ultrasonography in Detecting Abnormal Biopsy Findings in the Women Taking Estrogen Alone and in All the Women.

The circles and triangles show actual, unsmoothed values for sensitivity and specificity at the two thresholds for abnormal endometrial thickness (5 mm and 9 mm).

cohort, the choice between 5 and 9 mm reflects a compromise between sensitivity and specificity.

In a study of endometrial biopsies in 496 asymptomatic postmenopausal women, the prevalence rate for abnormal findings was 2 percent.[24] In a study of biopsies in 801 premenopausal and postmenopausal women, the prevalence of serious endometrial disease was 6 percent.[25] The 5 percent rate of disease in our study is similar to the rates in the other two studies. Although our study included one of the two women with adenocarcinoma in the overall PEPI study, about two thirds of the cases of endometrial disease detected in the larger study were diagnosed during the first half of the trial, before the start of the ultrasonography protocol. If the true prevalence of endometrial disease in asymptomatic women is higher, our estimates of positive predictive values may be low.

The negative predictive value for ultrasonography was high (99 percent) when the threshold for endometrial thickness was 5 mm. This high negative predictive value is not a justification for the use of ultrasonography in screening, since 53 percent of the women with normal biopsies had an endometrial thickness of at least 5 mm. But these results suggest that there is little additional information to be gained from an endometrial biopsy after an ultrasonographic examination has shown an endometrial thickness of less than 5 mm.

On the basis of an endometrial thickness of 5 mm or more, biopsies would have been indicated after more than half the ultrasonography examinations, but less than 10 percent of these examinations would have revealed serious endometrial disease. Because of the high false positive rate, ultrasonography is not a practical screening procedure in asymptomatic women, regardless of whether they are receiving estrogen-replacement therapy. Since the cost of transvaginal ultrasonography is similar to that of an endometrial biopsy, ultrasonography would offer no economic advantage, and half the women examined ultrasonographically would require a biopsy as a second procedure, which would erase the comfort-related benefit of the less invasive procedure and potentially cause anxiety about the possibility of disease.

As a procedure for monitoring the safety of unopposed-estrogen therapy, transvaginal ultrasonography was disappointing, with a low positive predictive value for detecting serious disease. Because of the high incidence of simple hyperplasia associated with increased endometrial thickness in women taking unopposed estrogen, a large fraction of such women would have to undergo a biopsy after ultrasonography.

Since bleeding is a cardinal symptom of endometrial disease, the prevalence of seriously abnormal histopathological findings was probably higher in the studies of women with bleeding than in the women we studied, most of whom were asymptomatic. Since the positive predictive value is influenced by the prevalence of disease, this disparity explains in part the contrast between our results and those of previous studies examining the usefulness of endometrial ultrasonography.

Supported by grants (U01-HL40154, U01-HL40185, U01-HL40195, U01-HL40205, U01-HL40207, U01-HL40231, U01-HL40232, and U01-HL40273) from the National Heart, Lung, and Blood Institute, the National Institute of Child Health and Human Development, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute of Diabetes and Digestive and Kidney Diseases, and the National Institute on Aging. Study medications were provided by Wyeth–Ayerst Laboratories, Philadelphia (Premarin), the Upjohn Company, Kalamazoo, Mich. (Provera), and Schering–Plough Research Institute, Kenilworth, N.J. (micronized progesterone).

APPENDIX

The following institutions and investigators participated in the Postmenopausal Estrogen/Progestin Interventions trial: George Washington University, Washington, D.C. — V.T. Miller and J. LaRosa; Johns Hopkins University, Baltimore — T. Bush and H. Zacur; Stanford University, Palo Alto, Calif. — P.D. Wood and M.L. Stefanick; University of California, Los Angeles — H.L. Judd and G. Greendale; University of California, San Diego, La Jolla — E. Barrett-Connor; University of Iowa, Iowa City — H.G. Schrott; University of Texas Health Science Center, San Antonio — C. Pauerstein; Bowman Gray School of Medicine, Winston-Salem, N.C. (coordinating center) — H.B. Wells, P. Hogan, and C. Wasilauskas; National Heart, Lung, and Blood Institute — I.L. Mebane-Sims; National Institute of Child Health and Human Development — J. Kelaghan; National Institute of Arthritis and Musculoskeletal and Skin Diseases — J. McGowan; National Institute of Diabetes and Digestive and Kidney Diseases — J. Fradkin; and National Institute on Aging — S. Sherman.

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