Effects of Hormone Replacement Therapy on Endometrial Histology in Postmenopausal Women

The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial

The Writing Group for the PEPI Trial

Objective.—To report the histological findings of the endometrium of postmenopausal women who were randomized to receive placebo, estrogen only, or one of three estrogen plus progestin (E+P) regimens in the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial.

Design.—A 3-year multicenter, randomized, double-masked, placebo-controlled trial.

Participants—A total of 596 postmenopausal women aged 45 through 64 years without contraindication to hormone therapy.

Intervention.—Participants were randomized and stratified in equal numbers to one of the following treatments in 28-day cycles: placebo, 0.625 mg/d of conjugated equine estrogens (CEE), 0.625 mg/d of CEE plus 10 mg/d of medroxyprogesterone acetate (MPA) for the first 12 days, 0.625 mg/d of CEE plus 2.5 mg/d of MPA, or 0.625 mg/d of CEE plus 200 mg/d of micronized progesterone (MP) for the first 12 days.

Outcome Measure.—Histology of endometrium collected at baseline, annual, or unscheduled visits by biopsy, curettage, or hysterectomy.

Analysis.—Intention to treat.

Results.—During follow-up women assigned to estrogen alone were more likely to develop simple (cystic), complex (adenomatous), or atypical hyperplasia than those given placebo (27.7% vs 0.8%, 22.7% vs 0.8%, and 11.8% vs 0%, respectively) for the same types of hyperplasia ($P<.001$). Participants administered one of the three E+P regimens had similar rates of hyperplasia as those given placebo ($P=.16$). The occurrence of hyperplasia was distributed evenly across the 3 years of the trial. Women taking estrogens alone also had more unscheduled biopsies (66.4% vs 8.4%; $P<.001$) and curettages (17.6% vs 0.8%; $P<.001$) than women receiving placebo. The number of surgical procedures was similar for women receiving placebo and women receiving the E+P regimens ($P=.38$). Of the 45 women with complex (adenomatous) or atypical hyperplasia, study medications were discontinued in all, and the biopsy results of 34 (94%) of 36 women with hyperplasia reverted to normal with progestin therapy. The remainder had dilatation and curettage (n=2) or hysterectomy with (n=2) or without (n=6) prior medical therapy, or refused further biopsies (n=1). One woman developed adenocarcinoma of the endometrium while receiving placebo.

Conclusions.—At a dosage of 0.625 mg, the daily administration of CEE enhanced the development of endometrial hyperplasia. Combining CEE with cyclic or continuous MPA or cyclic MP protected the endometrium from hyperplastic changes associated with estrogen-only therapy.

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From The Writing Group for the PEPI Trial.

A list of the members of The Writing Group for the PEPI Trial appears at the end of this article.

Dr Judd has received honoraria from Wyeth-Ayerst Laboratories, Philadelphia, Pa, producers of Premarin.

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ALTHOUGH estrogen replacement therapy for postmenopausal women has several known benefits, its long-term use has been associated with the development of endometrial cancer.[1-6] The major strategy to prevent this has been to administer a progestin in either a cyclic or a continuous pattern along with estrogen, and observational studies have supported this concept.[7-9] Although numerous investigations have reviewed the endometrial changes in women given estrogen plus a progestin (E+P), these studies have been flawed by design issues related to lack of proper controls, limited sample sizes, and short follow-up periods.[10-12]

The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial was a randomized, double-masked, placebo-controlled trial with 3 years of follow-up conducted to assess the influence of estrogen, with or without a progestin, on heart disease risk factors including high-density lipoprotein cholesterol, fibrinogen, insulin, and blood pressure in 875 women.[13] The trial also offered a unique opportunity to study the effect of hormone replacement therapies on the endometrium. This article reports the histological findings of the endometrium of 596 women with a uterus who were randomly assigned to placebo, estrogen only, or one of three E+P regimens in the PEPI trial.

METHODS

The study cohort consisted of 875 healthy postmenopausal volunteers of all races, 596 with and 279 without a uterus, between the ages of 45 and 64 years at entry who gave written informed consent to participate in the study. Additional information about the cohort has been presented elsewhere.[14-17] The data used herein are based on the results for the 596 women with a uterus who were randomly assigned to a study group.

The eligibility and exclusion criteria for this trial, reviewed elsewhere,[14] included cessation of menses at least 1 year but not more than 10 years prior to enrollment, a follicle-stimulating hormone level of at least 40 IU/L, and a normal or atrophic endometrial biopsy result at baseline. Women were excluded if they had breast or endometrial cancer, any other cancer except nonmelanomatous skin cancer diagnosed less than 5 years before baseline,

serious medical illness, or severe menopausal symptoms. Participants discontinued hormone replacement therapy 2 months prior to the first screening visit.

During prestudy evaluation, the participants underwent pelvic examination, Papanicolaou test, and endometrial biopsy or an attempted biopsy in which the operator was sure of entering the endometrial cavity. Women were eligible for randomization if the results of the above studies were normal.

Treatment Groups and Follow-up

Treatment group assignment was stratified by clinical center and uterine status and was assigned using a computer-generated randomization schedule developed and installed by the PEPI Coordinating Center. Women were randomized to one of the following treatments in 28-day cycles: placebo, 0.625 mg/d of conjugated equine estrogens (CEE), 0.625 mg/d of CEE plus 10 mg/d of medroxyprogesterone acetate (MPA) for the first 12 days, 0.625 mg/d of CEE plus 2.5 mg/d of MPA, or 0.625 mg/d of CEE plus 200 mg/d of micronized progesterone (MP) for the first 12 days.

All medications were taken orally for 3 years. Pills and capsules were provided in blister packs designed to be opened once a day. Active drugs and placebo were prepared in identical forms. The 2.5- and 10-mg doses of MPA were specially prepared for identical appearance. All women took two pills (one of CEE or matching placebo and one of MPA or matching placebo) daily and two capsules (each with 100 mg of MP or matching placebo) for the first 12 days of each cycle.

Records were maintained for all interruptions and discontinuations of study drug greater than 1 week. Clinic personnel filed a form indicating the dates when study drugs were discontinued and resumed. The compliance data were calculated using the data from these forms.

Scheduled visits occurred at 3, 6, and 12 months during the first year of the study and at 6-month intervals for the remainder of the 3-year study. At each visit, a diary of symptoms, reports of vaginal bleeding, medication use, and interim illnesses was reviewed. Unused pills were returned and counted to assess adherence. Included among the data collection and procedures at annual visits were pelvic examination, Papanicolaou test, and endometrial biopsy. Unscheduled visits were conducted as required to respond to problems noted by the participant or the local clinician.

Endometrial Biopsies

Endometrial tissue was obtained using standard biopsy techniques, without regard to the day of the woman's menstrual cycle. Most biopsies were performed with a Pipelle cannula and the remainder with vacuum or suction aspiration or a Novak-type curette. Biopsy results for women in whom the operator was certain of entry into the uterus but was unable to obtain tissue (due to presumed atrophy) were classified as normal. The 18 women in whom entry into the uterus was not possible at baseline were not assigned to a study group. If this occurred at follow-up visits, the woman discontinued study drugs (n=14). Unscheduled biopsies were performed to evaluate abnormal or problematic vaginal bleeding, or as a follow-up to an earlier diagnosis of hyperplasia.

Biopsy slides were reviewed by a local pathologist and then were reviewed by independent central readers. Slides with a discrepancy between the local and the central reading were reviewed by a third pathologist. In most cases the final diagnosis was based on agreement between two of the three pathologists. When there was disagreement among the three pathologists, the PEPI gynecologist who had reviewed the participant's clinical course selected the final diagnosis.

The following criteria were used for the diagnosis of the endometrial biopsies.[18] In *simple (cystic) hyperplasia*, there was an increase in both the stromata and the glandular elements. The glands were cystically dilated and lined by cuboidal proliferative cells without cytologic atypia. The glands were separated by a dense cellular stroma composed of ovoid cells with prominent nuclei. Small blood vessels were present. In *complex (adenomatous) hyperplasia*, there was a marked increase in the number of glands that appeared to be close together with little intervening stroma between them. The glands had a more complex architecture and could show out-pouching or budlike projections. These glands were lined by a stratified epithelium in which mitotic figures were occasionally present. The stromata were also very cellular and had mitotic figures. *Atypical hyperplasia* was characterized by the presence of cytologic atypia in the epithelium of the glands. The nucleus was larger and rounded and could have prominent nucleoli, and there were irregularities of the nuclear membrane. Occasional mitosis could be seen. In *adenocarcinoma*, there was marked cytologic atypia with large, prominent nuclei and a complex cribriform pattern. Necrosis, mitosis, and nuclear pleomorphism were present.

Some women underwent a dilatation and curettage (D&C) or a hysterectomy as part of the follow-up. In seven women, the result from a D&C or hysterectomy was more serious than the result from the previous biopsy. In these cases the diagnosis reported herein is based on the findings of these procedures and not on the results of an endometrial biopsy.

Unmasking Issues

Conditions requiring premature unmasking were limited to serious issues related to participant safety and are reported elsewhere.[13] The study protocol required unmasking for women with biopsy results classified as complex (adenomatous) hyperplasia, atypia, or cancer. Women with simple (cystic) hyperplasia were not unmasked. Only 38 women (6.4%) were completely unmasked, of whom 31 were receiving unopposed estrogen, three were receiving placebo, and four were receiving one of the E+P regimens.

Since vaginal bleeding may be a symptom requiring an intervention for participant safety, a mechanism for an unmasked review of bleeding data that maintained the masking of participants and clinical staff was required. A consulting gynecologist, not otherwise involved in the PEPI study, was notified the first time each woman experienced vaginal bleeding. This gynecologist reviewed the data about bleeding and then obtained from the PEPI Coordinating Center partial information on drug assignment indicating that the participant was receiving placebo, estrogen plus a sequential progestational agent, estrogen plus a continuous progestational agent, or estrogen only. After reviewing this information, the gynecologist gave a recommendation to the clinic staff, without revealing the drug assignment, on whether an unscheduled biopsy should be performed.

Follow-up for Endometrial Hyperplasia

Participants with a diagnosis of simple (cystic) hyperplasia continued to receive their study medications and had an endometrial biopsy within 6 months or at the next scheduled visit, whichever came first. Participants with a diagnosis of complex (adenomatous) or atypical hyperplasia had their study medications permanently discontinued and were offered three options for treatment: (1) The PEPI gynecologist would provide a 3-month course of 10 mg/d of MPA to reverse the hyperplasia, followed by an endometrial biopsy to assess the effect of the therapy; (2) the participant could seek care elsewhere at her own expense; or (3) the PEPI gynecologist and the participant could choose an alternative course of therapy. After treatment with one of these options, the participant was referred to her gynecologist for further care but was followed up for the remainder of the study by the PEPI investigators. The woman with adenocarcinoma had her study medications discontinued, was referred to a gynecologist for individualized management, and

Table 1.—Distribution of Endometrial Procedures Among Participants by Treatment Regimen*

Procedure	Treatment Regimen					Total
	Placebo	CEE Only	CEE + MPA (Cyclic)	CEE + MPA (Continuous)	CEE + MP	
Annual endometrial biopsy						
Baseline	119	119	118	120	120	596 (100%)
Follow-up visit, 12 mo	115	110	117	115	115	572 (96%)
Follow-up visit, 24 mo	112	104	112	111	110	549 (92%)
Follow-up visit, 36 mo	102	98	108	109	110	527 (88%)
Unscheduled biopsy†‡	11/10	115/79	20/16	11/9	17/14	174/128
D&C†§	1	24/21	2/2	1	0	28/25
Hysterectomy‖	2	7	3	0	2	14

*CEE indicates conjugated equine estrogens; MPA, medroxyprogesterone acetate; MP, micronized progesterone; and D&C, dilatation and curretage.
†Total number of procedures/number of women.
‡$P<.001$ for placebo compared with CEE only; $P=.38$ for placebo compared with CEE + MPA (cyc), CEE + MPA (con), and CEE + MP.
§$P<.001$ for placebo compared with CEE only; $P=.43$ for placebo compared with CEE + MPA (cyc), CEE + MPA (con), and CEE + MP.
‖$P=.04$ for overall comparison among groups.

Table 2.—Summary of Endometrial Biopsy Changes Since Normal Baseline to Most Extreme Abnormal Results, by Treatment Regimen*

Result	Treatment Regimen					Total, No. (%)
	Placebo	CEE Only	CEE + MPA (cyc)	CEE + MPA (con)	CEE + MP	
Normal†	116	45	112	119	114	506 (84.9)
Simple (cystic) hyperplasia‡	1	33	4	1	5	44 (7.4)
Complex (adenomatous) hyperplasia‡	1	27	2	0	0	30 (5.0)
Atypia‡	0	14	0	0	1	15 (2.5)
Adenocarcinoma	1	0	0	0	0	1 (0.2)
Total	**119**	**119**	**118**	**120**	**120**	**596 (100)**

*Includes 30 cases in which the diagnosis was assigned by the local gynecologist because the local, central, and arbiter pathologists gave different options. See the first footnote to Table 1 for expansions of the abbreviations.
†$P=.16$ (normal vs abnormal) for placebo compared with CEE + MPA (cyc), CEE + MPA (con), and CEE + MP.
‡$P<.001$ for placebo compared with CEE only.

was followed up by the PEPI investigators for the remainder of the study.

Statistical Analyses

All the analyses in this study were by intention to treat. Nominal P values are reported for comparisons between treatment regimens. Differences among treatment regimens for baseline characteristics were assessed with analysis of variance and the Fisher exact test. Frequencies and percentages describe the rates of events, and differences in rates among treatment regimens were assessed with the Fisher exact test. Log rank tests were used to compare the distributions of the time to diagnoses of hyperplasia among treatment regimens.

RESULTS

A total of 596 women with a uterus who were randomly assigned to the five treatment regimens had similar sociodemographic, lifestyle, and menopause-related characteristics.[17] Their average age was 56.2 years; 91% were white, 4% African American, 3% Hispanic, and 2% other. Their average body mass index was 25.7 kg/m^2. More than half had completed some college and had one, two, or three children. Forty-nine percent (292) had used estrogen and 25% (149) required a 2-month washout period. Fifty-nine percent (352) had used oral contraceptives. There were no statistically significant differences in these characteristics between groups.

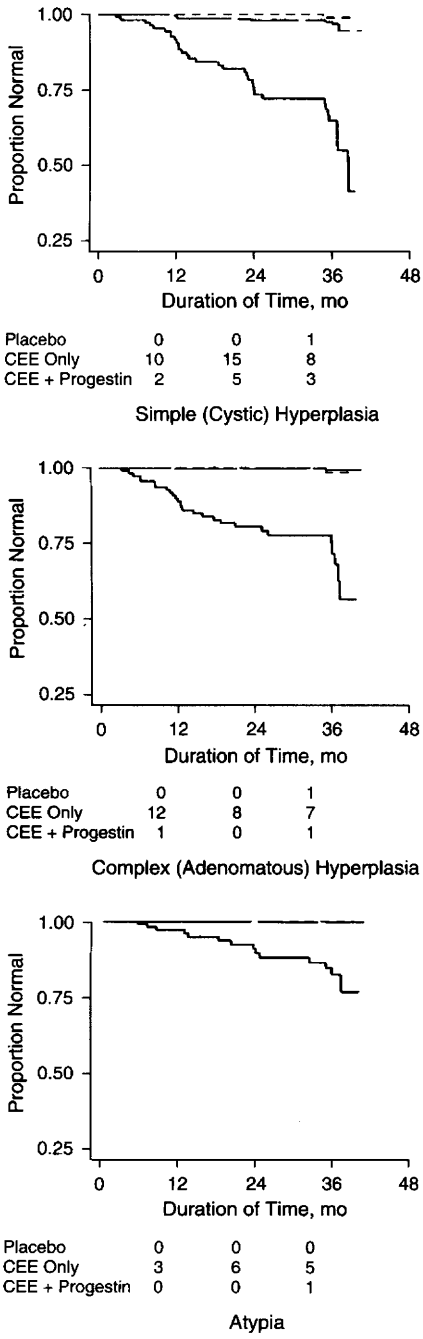
Records of interruptions in administration of the study drug were filed for participants who stopped taking their medications for more than a week. A total of 74.5% (444) of the women continued to take the study drug for at least 80% of the follow-up period. However, fewer of the participants assigned to CEE only (43.7% [52]) took the study drug for at least 80% of the follow-up period compared with 80% to 85% (96 to 102) of the participants in the other four groups ($P<.001$).

A summary of the number and types of procedures used to obtain samples of the endometrium during the course of the study is presented in Table 1. Approximately 120 endometrial biopsies were performed at baseline for each of the study groups. At the end of the 3-year trial, a total of 527 PEPI participants (88%) underwent biopsies. Although fewer women assigned to the CEE only group returned for their annual biopsies, there was no statistical difference between groups, because all participants were asked to have annual biopsies whether or not they continued to take the study drugs. Reductions in the number of annual biopsies for all groups were due to study dropouts or participants' refusal to have another biopsy.

A total of 174 unscheduled endometrial biopsies were performed. Ten (8.4%) of 119 women taking placebo had 11 unscheduled biopsies, while 79 (66.4%) of 119 women taking estrogen only had at least one unscheduled biopsy ($P<.001$). These 79 women had 66.1% (115/174) of all unscheduled biopsies. Among women taking one of the three E+P regimens, 16 (13.6%) taking cyclic MPA, nine (7.5%) taking continuous MPA, and 14 (11.7%) taking cyclic MP had unscheduled biopsies, rates that were similar to those of women receiving placebo ($P=.38$).

One woman receiving placebo had a D&C, whereas 21 participants receiving estrogen only therapy had a total of 24 D&Cs ($P<.001$). Women receiving the E+P regimens had zero to two D&Cs per regimen, similar to the rate of women receiving placebo ($P=.43$). There was a significant difference ($P=.04$) in the number of hysterectomies across all the treatment regimens. Two women taking placebo had hysterectomies during the trial, one for adenocarcinoma of the endometrium and one for an ovarian cystadenoma. Seven women taking CEE alone had hysterectomies, six for atypical hyperplasia and one for complex (adenomatous) hyperplasia. Five women receiving the E+P regimens had hysterectomies, one for atypical hyperplasia, one for persistent vaginal bleeding, two for uterine leiomyomas, and one for an ovarian cystadenoma.

Table 2 summarizes the endometrial histology results for the course of the study. Of the 2418 biopsies performed during the trial, 164 (6.7%) required the opinion of the arbiter pathologist. In 30 cases (1.2%), three different opinions were



Kaplan-Meier estimates of time to a diagnosis. The data below each graph show the number of annual cases of the same types of hyperplasia during follow-up according to the women's most abnormal endometrial biopsy result. The dotted line indicates placebo; solid line, CEE only; and broken line, CEE + progestin. CEE indicates conjugated equine estrogens.

reported and the diagnoses were assigned by the PEPI gynecologist.

The data presented in Table 2 represent the most abnormal endometrial histology result during follow-up for each participant. A total of 506 women (85%) had normal results for all follow-up biopsies. Endometrial hyperplasia or adenocarcinoma was reported for 90 women (15%). Among the 119 women assigned to placebo, one case each of simple (cystic) hyperplasia, complex (adenomatous) hyperplasia, and adenocarcinoma of the endometrium occurred. In women given CEE alone, 74 of 119 (62.2%) developed some type of endometrial hyperplasia and 41 of 119 (34.4%) had complex hyperplasia or atypia. These women were more likely to develop simple, complex, or atypical hyperplasia as their most abnormal diagnosis than women given placebo (27.7% vs 0.8%, 22.7% vs 0.8%, and 11.8% vs 0%, respectively; $P<.001$).

Ten cases of simple (cystic) hyperplasia, two of complex (adenomatous) hyperplasia, and one of atypical hyperplasia were distributed among the three E+P groups. There was no difference in the occurrence of abnormal biopsy specimens between the women who received placebo and those who received any of the three E+P regimens ($P=.16$).

The Figure shows the estimated survival functions of the time to the diagnosis of simple (cystic), complex (adenomatous), and atypical hyperplasia as the most abnormal biopsy result. The curves indicate the estimated proportion of women remaining free of a specific type of hyperplasia during a given length of time for placebo, estrogen alone, and the combined E+P regimens. The data show a significant difference in the hyperplasia-free intervals among the regimens ($P<.001$). Women in the placebo and E+P groups had longer intervals free of all three types of hyperplasia than women in the CEE only group. The data below each graph show the number of women who developed hyperplasia during each year of follow-up. For the CEE only group, 25 (21%), 29 (24.4%), and 20 (16.8%) women developed some type of hyperplasia as their most abnormal result during the first, second, and third years of the study, respectively. Of these women, 15 (12.5%), 14 (11.8%), and 12 (10.1%) had the more concerning diagnosis of complex (adenomatous) or atypical hyperplasia for the same respective years. There was no discernible pattern in the occurrence of hyperplasia in the other treatment groups.

Table 3 shows the status at the last follow-up visit, by most abnormal diagnosis, for all women who developed endometrial hyperplasia or cancer during the study. Among the 44 women with simple (cystic) hyperplasia as their most abnormal diagnosis, five (11%) persisted with this diagnosis at subsequent biopsies; the biopsy results of 38 women (86%) reverted to normal (18 spontaneously and 20 with intervention) and one (2%) had incomplete follow-up data. Of the interventions, 15 consisted of cessation of study medications with (n=5) or without (n=10) a D&C. Five other women received a progestin administered at the end of follow-up for diagnoses made at the 3-year visit. An additional 11 women had simple (cystic) hyperplasia but progressed to a more serious form of hyperplasia and are included in those categories (Table 3).

Among the 30 women with complex (adenomatous) hyperplasia as their most abnormal diagnosis, study medications were discontinued in all according to protocol. Most were given progestin with (n=4) or without (n=22) D&Cs, and their endometrial biopsy results reverted to normal. Two women underwent D&C alone and subsequent biopsies were normal, one woman underwent a hysterectomy without prior medical therapy, and one was treated by her private physician and refused further biopsies.

Among the 15 women who developed atypical hyperplasia, seven received progestin and one received progestin and underwent a D&C. All had endometrial biopsy results that reverted to normal. Seven other women had hysterectomies, of whom two were given progestin before surgery that failed to convert their endometrial biopsy results to normal.

The 24-month biopsy specimen of the woman who developed endometrial cancer while receiving placebo was interpreted by the local pathologist as atypical hyperplasia, by the central pathologist as chronic endometritis, possibly hyperplasia, and by the arbiter as menstrual endometrium with metaplasia and focal simple atypical hyperplasia. The biopsy specimen was coded as atypical hyperplasia, and the participant was unmasked. Her local physician performed a D&C, which revealed acute and chronic endometritis. Her 3-year biopsy specimen showed well-differentiated grade I adenocarcinoma. A hysterectomy and bilateral salpingo-oophorectomy were performed and confirmed the diagnosis. As of June 10, 1993, the patient had remained free of disease since surgery.

COMMENT

The design of the PEPI trial was determined primarily by consideration of the effect of ovarian hormone replacement on cardiovascular disease risk factors. Treatment with daily CEE was considered essential since numerous observational studies conducted in the United States have reported that this preparation reduces heart disease risk by approximately 50%.[19-21] Medroxyprogesterone acetate was chosen for study because it is the most commonly used preparation for endometrial protection in postmenopausal women in this country.[22] The 10-mg dosage was selected because it has been reported to reduce endometrial epithelial DNA synthesis (thymidine labeling index) and to induce secretory transformation

Table 3.—Final Status of Participants With Abnormal Endometrial Biopsy Results According to Their Most Abnormal Result, by Treatment Regimen*

	Most Extreme Abnormal Result								
	Simple (Cystic) Hyperplasia			Complex (Adenomatous) Hyperplasia			Atypical Hyperplasia		
Status	Placebo	CEE Only	CEE + P†	Placebo	CEE Only	CEE + P†	Placebo	CEE Only	CEE + P†
No change	0	4	1	0	0	0	0	0	0
Reversion to normal									
Spontaneous	0	12	6‡	0	0	0	0	0	0
Intervention§	1	16	3	1	25	2	0	8	0
Hysterectomy	0	0	0	0	1	0	0	6	1
Unknown	0	1	0	0	1	0	0	0	0
Total	**1**	**33**	**10**	**1**	**27**	**2**	**0**	**14**	**1**

*One participant in the placebo group developed adenocarcinoma and underwent hysterectomy. See the first footnote to Table 1 for expansions of the abbreviations.
†All other active regimens.
‡The biopsy results of one participant reverted to normal, and she had a hysterectomy later in the study.
§Intervention may include discontinuation of a study drug and/or a variety of other therapies.

more than the 2.5- and 5-mg dosages.[23] The 12-day duration of MPA and MP administration per 28-day cycle was selected because of reports that this duration reduced the occurrence of endometrial hyperplasia more than administration for 7 or 10 days.[24] The continuous 2.5-mg MPA regimen was selected because of reports that it induced amenorrhea and had been shown to prevent hyperplasia in a limited trial.[25] Micronized progesterone was selected because preliminary data suggested this medication did not mask the estrogen-mediated increase in high-density lipoprotein cholesterol.[26,27]

To conduct the PEPI trial, a strategy had to be devised to assess the effects of these hormone replacement therapies on the endometrium. The strategy chosen was to obtain baseline and annual endometrial biopsy specimens and to monitor participants for the development of endometrial hyperplasia, particularly complex (adenomatous) or atypical hyperplasia. These diagnoses were viewed as prognostic markers of the possible future development of cancer based on reports of women with these diagnoses who did not undergo hysterectomy. Previous studies have shown that 3% to 75% of women developed endometrial cancer subsequent to the diagnosis of hyperplasia, depending on the length of follow-up and the severity of hyperplasia at the time of the original diagnosis.[28-33]

In the group given placebo, one case each of simple (cystic) hyperplasia, complex (adenomatous) hyperplasia, and adenocarcinoma of the endometrium developed during the 3 years of follow-up. The occurrence of complex hyperplasia was probably hormone induced because the participant discontinued placebo after only 2 months and took CEE and MPA prescribed by her private physician.

Among the 119 women in the CEE only group, 74 (62%) developed some type of endometrial hyperplasia during follow-up, with 41 women (34%) displaying the more serious diagnoses of complex (adenomatous) hyperplasia or atypia. This accounted for the lower rate of compliance (43.7%) with study medications in the CEE only vs the other groups. Six of the participants receiving CEE alone were diagnosed with simple hyperplasia with atypia based on the reading of the arbiter pathologist, whereas the local and central pathologists did not identify atypia. The decision of the PEPI gynecologist to assign the most severe diagnosis of those presented to him or her probably reflected concern for women in a randomized trial.

The statistically significant increase of endometrial hyperplasia in women given CEE alone in this direct comparison with placebo unequivocally established this as a risk of CEE only therapy at this dosage. This conclusion was reinforced by the finding of normal endometrium in both groups at baseline. Based on the timing of the occurrence of the most abnormal biopsy result in each participant (Figure), the development of all three types of hyperplasia remained constant across the 3 years of treatment. If the yearly occurrence of hyperplasia persisted in subsequent years, it would be anticipated that a majority of women taking CEE alone would have the more serious types of complex (adenomatous) or atypical hyperplasia after about 5 years of therapy. This finding raises serious questions about the safety of long-term CEE only therapy in women with a uterus. In the only comparable study, Woodruff et al[12] reported incidences of cystic hyperplasia of 19% and complex hyperplasia of 0.7% in 283 women randomized to the same dose of CEE given daily for only 1 year. No participant with atypical hyperplasia was identified. This study did not include a placebo group for comparison to CEE alone.

What were the long-term implications of hyperplasia among the participants taking CEE alone? First, in regard to hyperplasia, medical intervention, when attempted, converted the endometrium to normal in all participants with simple (cystic) and complex (adenomatous) hyperplasia. In women with atypical hyperplasia, medical intervention was effective in eight of 10 women in whom it was tried. Comparable results have been reported by Thom et al.[33] Second, in regard to surgical interventions, more procedures were performed during follow-up of women receiving CEE alone than were needed in the other groups. This included unscheduled biopsies (66% of total procedures), D&Cs (86% of total procedures), and hysterectomies (50% of total procedures). During review of the participant's first bleeding episode, the monitoring gynecologist was partially unblinded to treatment assignment. It was likely that concern for women receiving CEE only therapy contributed to the more frequent recommendation of these diagnostic procedures. Of the seven hysterectomies performed in the women given CEE alone, medical therapy was attempted only once and failed. Whether medical therapy would have been effective in controlling vaginal bleeding and reverting the hyperplasia to normal in the other participants is unknown. However, medical therapy was successful in reverting the endometrium to normal in 97% of women receiving CEE alone (31/32) who developed complex (adenomatous) or atypical hyperplasia. Based on these findings, we would recommend that physicians use medical intervention in women undergoing hormone replacement who develop complex (adenomatous) or atypical hyperplasia before considering a surgical intervention such as a hysterectomy.

In women given E+P, the incidence of abnormal biopsy results was comparable to that observed among women receiving placebo. All E+P regimens were effective in preventing hyperplasia to the extent observed in women receiving placebo. Similar endometrial protection has been reported for 5 or 10 mg of MPA given for 14 days each month and 2.5 or 5 mg given continuously with CEE for 1 year.[12] In addition, the numbers of surgical procedures required among these participants were also similar to the number performed in the placebo group. The results of our 3-year trial indicate that these

specific progestin regimens provide long-term endometrial protection of postmenopausal women with a uterus. Whether other progestins, other doses of the same progestins, or other progestin regimens are as effective in preventing endometrial hyperplasia awaits further study.

The PEPI study design provided for participants to continue to receive study medications with more frequent endometrial biopsies following a diagnosis of simple (cystic) hyperplasia. Among the 55 women who were ever diagnosed with simple (cystic) hyperplasia, the majority (77%) subsequently had normal endometrial biopsy results spontaneously or with intervention, but 20% advanced to more serious lesions while receiving CEE alone or combined therapy. If hormone replacement is continued in women with simple (cystic) hyperplasia, it should be anticipated that some women will develop more serious lesions. Thus, caution should be exercised in following this approach.

We conclude that physicians who provide estrogen replacement therapy for postmenopausal women with a uterus should give serious consideration to the addition of a progestin administered either cyclically or continuously for endometrial protection. In women who cannot tolerate or use progestins, CEE only therapy can be considered, but follow-up should include annual endometrial assessment with cessation of this regimen following the diagnosis of endometrial hyperplasia. If hyperplasia is found in women receiving estrogen replacement therapy, most endometrial hyperplasia will revert to normal with prolonged progestin administration.

The Writing Group for the PEPI Trial includes Howard L. Judd, MD, chair; Irma Mebane-Sims, PhD; Claudine Legault, PhD; Carol Wasilauskas, MS; Susan Johnson, MD; Maria Merino, MD; Elizabeth Barrett-Connor, MD; and Jose Trabal, MD.

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A complete list of members of the PEPI Trial Group appears elsewhere.[13] The following list acknowledges persons primarily responsible for the collection of the endometrial-related data.

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