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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.

Abstract
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 un-

scheduled 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.