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JAMA. 1995 Jan 18;273(3):199-208.

Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial.

[No authors listed]

Erratum in
JAMA 1995 Dec 6;274(21):1676.

Abstract

OBJECTIVE: To assess pairwise differences between placebo, unopposed estrogen, and each of three estrogen/progestin regimens on selected heart disease risk factors in healthy postmenopausal women.

DESIGN: A 3-year, multicenter, randomized, double-blind, placebo-controlled trial.

PARTICIPANTS: A total of 875 healthy postmenopausal women aged 45 to 64 years who had no known contraindication to hormone therapy.

INTERVENTION: Participants were randomly assigned in equal numbers to the following groups: (1) placebo; (2) conjugated equine estrogen (CEE), 0.625 mg/d; (3) CEE, 0.625 mg/d plus cyclic medroxyprogesterone acetate (MPA), 10 mg/d for 12 d/mo; (4) CEE, 0.625 mg/d plus consecutive MPA, 2.5 mg/d; or (5) CEE, 0.625 mg/d plus cyclic micronized progesterone (MP), 200 mg/d for 12 d/mo. PRIMARY ENDPOINTS: Four endpoints were chosen to represent four biological systems related to the risk of cardiovascular disease: (1) high-density lipoprotein cholesterol (HDL-C), (2) systolic blood pressure, (3) serum insulin, and (4) fibrinogen.

ANALYSIS: Analyses presented are by intention to treat. P values for primary endpoints are adjusted for multiple comparisons; 95% confidence intervals around estimated effects were calculated without this adjustment.

RESULTS: Mean changes in HDL-C segregated treatment regimens into three statistically distinct groups: (1) placebo (decrease of 0.03 mmol/L [1.2 mg/dL]); (2) MPA regimens (increases of 0.03 to 0.04 mmol/L [1.2 to 1.6 mg/dL]); and (3) CEE with cyclic MP (increase of 0.11 mmol/L [4.1 mg/dL]) and CEE alone (increase of 0.14 mmol/L [5.6 mg/dL]). Active treatments decreased mean low-density lipoprotein cholesterol (0.37 to 0.46 mmol/L [14.5 to 17.7 mg/dL]) and increased mean triglyceride (0.13 to 0.15 mmol/L [11.4 to 13.7 mg/dL]) compared with placebo. Placebo was associated with a significantly greater increase in mean fibrinogen than any active treatment (0.10 g/L compared with -0.02 to 0.06 g/L); differences among active treatments were

not significant. Systolic blood pressure increased and postchallenge insulin levels decreased during the trial, but neither varied significantly by treatment assignment. Compared with other active treatments, unopposed estrogen was associated with a significantly increased risk of adenomatous or atypical hyperplasia (34% vs 1%) and of hysterectomy (6% vs 1%). No other adverse effect differed by treatment assignment or hysterectomy status.

CONCLUSIONS: Estrogen alone or in combination with a progestin improves lipoproteins and lowers fibrinogen levels without detectable effects on postchallenge insulin or blood pressure. Unopposed estrogen is the optimal regimen for elevation of HDL-C, but the high rate of endometrial hyperplasia restricts use to women without a uterus. In women with a uterus, CEE with cyclic MP has the most favorable effect on HDL-C and no excess risk of endometrial hyperplasia.

Comment in

PEPI in perspective. Good answers spawn pressing questions. [JAMA. 1995]
The Postmenopausal Estrogen/Progestin Interventions Trial. [JAMA. 1995]
The Postmenopausal Estrogen/Progestin Interventions Trial. [JAMA. 1995]

PMID: 7807658 [PubMed - indexed for MEDLINE]

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