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Effects of estradiol with micronized progesterone or medroxyprogesterone acetate on risk markers for breast cancer in postmenopausal monkeys

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Abstract

The addition of the synthetic progestin medroxyprogesterone acetate (MPA) to postmenopausal estrogen therapy significantly increases breast cancer risk. Whether this adverse effect is specific to MPA or characteristic of all progestogens is not known. The goal of this study was to compare the effects of oral estradiol (E2) given with either MPA or micronized progesterone (P4) on risk biomarkers for breast cancer in a postmenopausal primate model. For this randomized crossover trial, twenty-six ovariectomized adult female cynomolgus macaques were divided into social groups and rotated randomly through the following treatments (expressed as equivalent doses for women): (1) placebo; (2) E2 (1 mg/day); (3) E2 + P4 (200 mg/day); and (4) E2 + MPA (2.5 mg/day). Hormones were administered orally, and all animals were individually dosed. Treatments lasted two months and were separated by a one-month washout period. The main outcome measure was breast epithelial proliferation, as measured by Ki67 expression. Compared to placebo, E2 + MPA resulted in significantly greater breast proliferation in lobular ($P < 0.01$) and ductal ($P < 0.01$) epithelium, while E2 + P4 did not. Intramammary gene expression of the proliferation markers Ki67 and cyclin B1 was also higher after treatment with E2 + MPA ($P < 0.01$) but not E2 + P4. Both progestogens significantly attenuated E2 effects on body weight, endometrium, and the TFF1 marker of estrogen receptor activity in the breast. These findings suggest that oral micronized progesterone has a more favorable effect on risk biomarkers for postmenopausal breast cancer than medroxyprogesterone acetate.