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Novel oral, continuous-combined solubilized 17?-estradiol and natural progesterone provides endometrial protection: Comparison of two randomized controlled trials

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Context: The incidence of endometrial cancer may be different with medroxyprogesterone acetate (MPA) vs natural progesterone (P4) when used with estrogens for endometrial protection. The WHI reported a lower incidence of endometrial cancer vs placebo in women using 0.625 mg/day conjugated equine estrogens (CEE) and 2.5 mg/day MPA followed for a median intervention of 5.6 years and median cumulative follow-up of 13 years [1]. The REPLENISH trial showed for the first time [3-5] that P4 continuously combined with 17?-estradiol (E2) provides adequate endometrial protection [2].
Objective: To compare the separately conducted REPLENISH and Women's HOPE trials in terms of endometrial protection and uterine bleeding.
Methods: The REPLENISH (NCT01942668) study was a 12-month, randomized, double-blind, placebo-controlled, multicenter trial that examined an investigational continuous-combined oral E2/P4 (TX-001HR, TherapeuticsMD, Inc) for the treatment of moderate-to-severe vasomotor symptoms in menopausal women [2]. The Women's HOPE trial [6,7] was a 12-month, randomized, double-blind, placebo-controlled, multicenter trial that evaluated continuous-combined CEE/MPA in menopausal women. Endometrial biopsies were performed and evaluated similarly in both studies.
Patients: Menopausal women with an intact uterus.
Interventions: Continuous-combined, oral E2/P4 (1.0 mg/100 mg, 0.5 mg/100 mg, 0.5 mg/50 mg, 0.25 mg/50 mg) [2], or CEE/MPA (0.625 mg/2.5 mg, 0.45 mg/2.5 mg, 0.45 mg/1.5 mg, 0.3 mg/1.5 mg) [6,7].
Main Outcome Measure: Comparison of endometrial hyperplasia and uterine bleeding data.
Results: Incidence rates of endometrial hyperplasia at 12 months were below 1% with all doses evaluated in both REPLENISH and Women's HOPE trials. Cumulative amenorrhea rates with E2/P4 at 12 months were high (56–73% vs 81% with placebo) and had increased over time; rates with CEE/MPA ranged from 22–45% vs 68% with placebo.
Conclusions: When given continuously, specific combinations/doses of solubilized E2 and P4 provided endometrial protection (similar to MPA) and resulted in favorable amenorrhea rates.
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