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Effects of Tibolone and Continuous Combined Conjugated Equine Estrogen/Medroxyprogesterone Acetate on the Endometrium and Vaginal Bleeding: Results of the OPAL Study

Robert D. Langer, MD, MPH,[a,*] Britt Marie Landgren, MD,[b] Janice Rymer, MD,[c] Frans A. Helmond, PhD,[d] for the OPAL Investigators

Gesinger Health System,[a] Danville, PA; Karolinska Hospital and Institutet,[b] Stockholm, Sweden; Guy's, King's, and St Thomas' School of Medicine, King's College,[c] London, UK; Organon International,[d] Roseland, NJ

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KEY WORDS
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Objectives: The primary objective of the **O**steoporosis **P**revention and **A**rterial effects of tibo-**L**one study was to compare the effect of tibolone and placebo on the progression of the common carotid artery intima-medial thickness; the common carotid artery intima-medial thickness and bone data will be presented elsewhere. A secondary objective was to assess the effects of tibolone (2.5 mg), continuous combined conjugated equine estrogen/medroxyprogesterone acetate [0.625/2.5 mg], and placebo on the endometrium and vaginal bleeding; these results are the subject of this report.

Study design: This 3-year, three-arm, international, randomized, double-blind, parallel group, placebo-controlled clinical trial enrolled 866 postmenopausal women (aged 45-79 years). The endometrium was assessed by annual transvaginal ultrasound scans and end-of-study biopsies (United States/United Kingdom centers only). Vaginal bleeding was recorded in daily diaries.

Results: Endometrial thickness measured by transvaginal ultrasound scan increased slightly during the first year with tibolone and conjugated equine estrogen/medroxyprogesterone acetate, without any further progression. After 3 years, there were no significant differences between the tibolone, conjugated equine estrogen/medroxyprogesterone acetate, and placebo groups in the incidence of proliferation (1.4%, 4.8%, and 0%, respectively), endometrial hyperplasia (0% in all groups), or cancer (1, 0, and 1 case, respectively). During the first 3 months, bleeding/spotting rates were greater with conjugated equine estrogen/medroxyprogesterone acetate (48%) than with tibolone (18%; $P < .001$) or placebo (3%; $P < .001$). During 3 years of treatment, the incidence of bleeding/spotting was 66%, 48%, and 23% for conjugated equine estrogen/medroxyprogesterone acetate, tibolone, and placebo, respectively. The mean number of bleeding/spotting days was greater in the conjugated equine estrogen/medroxyprogesterone acetate than the tibolone

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* Reprint requests: Robert D. Langer, MD, MPH, Center for Health Research & Rural Advocacy, Geisinger Health System, 100 N Academy Avenue, Danville, PA 17822-3003.
E-mail: rdlanger@geisinger.edu

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or placebo groups (61, 28, and 7 days, respectively; $P = .023$ vs tibolone; $P < .0001$ vs placebo). The mean number of bleeding/spotting episodes was also greater in the conjugated equine estrogen/medroxyprogesterone acetate group (13 episodes) compared with the tibolone group (six episodes; $P < .001$) and placebo group (four episodes; $P < .001$). Vaginal bleeding was more commonly reported as an adverse event with conjugated equine estrogen/medroxyprogesterone acetate than tibolone (26.4% vs 10.8%, $P < .0001$) and as the reason for premature discontinuation (9% vs 2%, $P = .001$).

Conclusion: Compared with conjugated equine estrogen/medroxyprogesterone acetate, tibolone has a better tolerability profile with respect to vaginal bleeding but with a similar endometrial safety. These results reinforce the endometrial safety profile of tibolone.

Conjugated equine estrogen (CEE) plus medroxyprogesterone acetate (MPA) is one of the most commonly used estrogen-progestogen therapy (EPT) combinations and its endometrial safety has been confirmed in large-scale studies.[1-3] However, it has been associated with frequent bleeding and spotting episodes, especially in the first 6 months of treatment.[4] Tibolone is a selective tissue estrogenic activity regulator[5] that is effective in the prevention of osteoporosis and treatment of climacteric symptoms and does not stimulate endometrial and breast tissue.[6] In the endometrium, tibolone locally reduces estrogenic activity via two different routes. Tibolone decreases the activity of the enzyme sulfatase and increases the activity of the enzyme sulfotransferase. These two enzymes are involved in the activation and deactivation, respectively, of estrogenic compounds, resulting in a shift toward deactivation. The other route is the metabolization of the two estrogenic hydroxymetabolites of tibolone back into tibolone, which can be further metabolized locally into the Δ^4-isomer, which has progestogenic but no estrogenic properties.[7-9] Tibolone is associated with a low incidence of endometrial hyperplasia and vaginal bleeding and does not require the addition of a progestogen.[10-16]

The Osteoporosis Prevention and Arterial effects of tiboLone (OPAL)[17] study was conducted to determine the effects of tibolone, continuous combined CEE/MPA, and placebo on bone mineral density and carotid intima-media thickness (CIMT) in postmenopausal women. This double-blind placebo-controlled trial also captured unique long-term (3 years) comparative data on endometrial safety and vaginal bleeding for tibolone and CEE/MPA.

Methods

This three-arm, multicenter, randomized, double-blind, placebo-controlled study was conducted in six centers in the United States (US) and five centers in Europe. Healthy postmenopausal women (aged 45-79 years and with a body mass index of >19 and ≤ 32 kg/m^2) who had been amenorrheic for ≥ 1 year were enrolled. If the date of final menstruation was unclear, the woman was to have used hormone therapy (HT) for >2 years and be >53 years old or fulfill the US Food and Drug Administration (FDA) criteria for menopause (serum estradiol ≤ 20 pg/mL [or 73 pmol/L] and follicle-stimulating hormone ≥ 40 mIU/mL). Per study protocol, an intact uterus was required for enrollment in the US centers, whereas in European centers, women with or without a uterus were eligible. A washout period of 8 weeks was required for oral estrogens with or without progestogens, androgens, or selective estrogen receptor modulators (SERMs), 4 weeks for transdermal or local sex steroids, and 20 weeks for injections of MPA-containing contraceptives. Women were excluded if they had an abnormal cervical Pap smear result, double-layer endometrial thickness of >5 mm as measured by transvaginal ultrasound scan (TVUS), endometrial hyperplasia, unexplained vaginal bleeding that required follow-up, uncontrolled hypertension, current or recent alcohol and/or drug abuse, Type I diabetes mellitus, low total fasting cholesterol, recent history of myocardial infarction, heart failure requiring pharmacologic treatment, current or previous stroke, thrombophlebitis, thromboembolic disorder, gallbladder disease or malignancy (except nonmelanoma skin cancer), suspected breast malignancy, relevant abnormal electrocardiogram (ECG) or laboratory values, serious decompensated renal or liver disease, a carotid ultrasound alert, carotid arteries that were difficult to image using the study protocol, any condition that could alter the pharmacokinetics of the investigational drugs, or hypersensitivity to tibolone or CEE/MPA. Current or recent prolonged use of systemic corticosteroids or hepatic microsomal enzyme-inducing anticonvulsant medication (or other drugs known to alter the pharmacokinetics of steroids), investigational drug use within the last 60 days, a requirement for medication to treat or prevent dyslipidemia and/or osteoporosis, or a requirement for sex steroids, androgens, or SERMs were also reasons for exclusion.

All women provided written informed consent according to the regulations at each participating institution. The study was conducted according to Good Clinical Practice, in full compliance with the Declaration of Helsinki including revisions, and the protocol was