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A 5-year study on the effect of hormone therapy, tibolone and raloxifene on vaginal bleeding and endometrial thickness

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Abstract

Objectives: To study the effect of standard and low-dose estrogen–progestin therapy (EPT), tibolone and raloxifene on the incidence of vaginal spotting/bleeding and endometrial thickness over a 5-year period.

Methods: Seven hundred eighty-six postmenopausal women were studied in an open prospective design. Vaginal spotting/bleeding and endometrial thickness as assessed by transvaginal ultrasonography was compared between six categories of women over a 5-year period: three categories in women on continuous combined estrogen–progestin therapy, one category under tibolone, one category under raloxifene and one under no treatment. More specifically, women received tibolone 2.5 mg ($N = 204$), raloxifene HCl 60 mg ($N = 137$), conjugated equine estrogens 0.625 mg/medroxyprogesterone acetate 5 mg ($N = 122$), 17β-estradiol 2 mg/norethisterone acetate 1 mg ($N = 58$), 17β-estradiol 1 mg/norethisterone acetate 0.5 mg ($N = 76$) or no therapy (controls, $N = 189$). Women with suspected endometrial pathology were referred for hysteroscopy.

Results: Bleeding/spotting incidence was highest among standard dose EPT users (conjugated equine estrogens 0.625 mg/medroxyprogesterone acetate 5 mg: 40.1%, 17β-estradiol 2 mg/norethisterone acetate 1 mg: 44.8%, $p < 0.001$ compared to controls). Low-dose EPT associated with lower incidence of spotting/bleeding (34.1%). The incidence under tibolone and raloxifene was 22.5% and 2.9%, respectively, while 3.2% of women not receiving therapy reported vaginal spotting/bleeding. Mean endometrial thickness was not significantly affected in any of the groups studied. The drop-out rate due to spotting/bleeding was higher in the two higher dose EPT regimens. After logistic regression analysis, age at baseline was the only significant predictor of subsequent spotting/bleeding ($b = -0.25$, S.E. = 0.09, $p = 0.006$), while menopausal age and pre-treatment serum FSH had marginal significance.

Conclusions: EPT, tibolone and raloxifene do not appear to associate with significant changes in endometrial thickness in the majority of cases. The low-dose EPT regimen associated with a decreased incidence of unscheduled spotting/bleeding compared to the standard dose regimens. Tibolone expressed a favorable endometrial profile, as seen in its effect on unscheduled

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spotting/bleeding and mean endometrial thickness. Raloxifene associated with the lowest incidence in S/B and the lowest drop-out rate.s

Keywords: Endometrial thickness; Vaginal bleeding; Estradiol; Conjugated equine estrogen; Progestin; Tibolone; Raloxifene

1. Introduction

Hormone therapy (HT) is given to postmenopausal women for the relief from climacteric symptoms and the prevention of urogenital atrophy. Furthermore, prolonged HT administration has been associated with an osteoprotective effect [1]. In non-hysterectomized women estrogen is combined with a progestin (EPT), so as to offset the proliferative effect of estrogen on the endometrium and minimize the risk for hyperplasia-cancer. In fact, this combined regimen given continuously eventually induces endometrial atrophy and amenorrhea [2–4]. The recently published results from the Million Women Study indicate a reduced risk of endometrial cancer in women under continuous combined EPT [5]. However, endometrial safety during long-term EPT is still not established and even an optimal estrogen/progestin dose ratio may expose the endometrium to pathology. Sporadic cases of endometrial cancer have been reported among women on continuous EPT [6–8].

Continuous EPT may cause vaginal spotting/bleeding (S/B) mainly during the initial 6–9 months of therapy in up to 60% of women [9,10]. Although unscheduled S/B during EPT is not necessarily an indicator or predictor of endometrial pathology [11,12], its absence does not always exclude the presence of a lesion [13]. Monitoring the endometrium under long-term EPT is advisable in women presenting with S/B. Routine invasive evaluation of the endometrium in HT users is not indicated, for it will affect their decision to initiate or adhere to therapy. Transvaginal sonography (TVS) is a non-invasive and reliable method for evaluating the uterus and endometrium at baseline and for monitoring the effect of HT on endometrium particularly in the presence of unscheduled S/B [12,13].

The results of WHI [14] have led to a re-appraisal of the indications for HT and the reported effect on breast cancer and cardiovascular disease incidence has obliged us to consider HT regimens of lower dose than that administered in WHI, as well as alternative therapies to deal with the consequences of estrogen depletion. Tibolone is a synthetic steroid with tissue-specific action. Following rapid conversion to the 3α- and 3β-hydroxy-metabolites and the Δ4 isomer, tibolone may engage either the ER-α, expressing estrogenic activity or the progesterone and androgen receptors and act as a progestogen–androgen [15]. As such tibolone has been extensively administered in Europe as an effective alternative to HT in treating climacteric symptoms and vaginal atrophy, in improving libido and in preventing bone loss [16], while having minimal stimulatory effect on the breast [17,18] and endometrium [19,20]. This data, however, comes from observational studies, while results from randomized controlled trials are still missing.

Raloxifene, a non-steroid benzothiophene derivative is classified as a selective estrogen receptor modulator (SERM). Although devoid of any action on climacteric symptoms and vaginal atrophy, raloxifene expresses an estrogen-agonist effect on the skeleton [21,22] and cardiovascular risk factors [21,23–25], while being an estrogen antagonist on the breast [26,27] and endometrium [21,22,28]. Raloxifene administration in osteoporotic women with a high-risk profile for cardiovascular disease appears to decrease the incidence of cardiovascular events compared to the placebo group [29].

The purpose of this study was to assess the effect of various continuous EPT regimens, tibolone and raloxifene on the incidence of unscheduled S/B and endometrial thickness.

2. Materials and methods

Seven hundred eighty-six postmenopausal women with an intact uterus aged 42–66 years were included in the study. Subjects were recruited from the Menopause Clinic of the 2nd Department of Obstetrics and Gynecology, University of Athens, Aretaieion Hospital between September 1997 and December 1999. Patients