New Selective Tissue Estrogenic Activity Regulator (STEAR) in Menopausal Therapy in Taiwan

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SUMMARY

Objective: The compliance of women living in Taiwan with the selective tissue estrogenic activity regulator (STEAR) tibolone has seldom been reported. The purpose of this study was to evaluate the short-term compliance of perimenopausal women living in Taiwan in taking tibolone, and the efficacy of the drug.

Materials and Methods: A total of 289 perimenopausal women who had experienced mild to severe climacteric symptoms were enrolled in this study. Every woman was evaluated before (baseline), during (end of the third month), and after therapy (end of the sixth month) with 2.5 mg tibolone daily. Efficacy was assessed from improvement in climacteric symptoms and compliance was also assessed.

Results: A total of 275 women were still on tibolone treatment by the end of the study, revealing a high rate (95.2%) of retention. Breast tenderness was significantly reduced, from 26.5% to 2.8%. The reported rate of insomnia was 50.5% at baseline, and had been reduced to 20.4% by the end of the study. Bleeding episodes dropped from 87.4% at baseline to 39.4% at the end of the study. The rate of mood instability was significantly reduced, from 84.1% at baseline to 44.3% at the end of the study. Libido improved from 15.9% at baseline to 61.6% at the end of the study, a unique benefit of tibolone due to the androgenic effect of its δ-isomer. Most women (84.1%) had an increase in body weight ranging from 0.5 to 3 kg. Fourteen subjects dropped out for the following reasons: three women had acne and/or allergic reaction, four had a significant increase in body weight and/or water retention, one had headache, and the other six dropped out for personal reasons.

Conclusion: Tibolone can improve the climacteric symptoms of perimenopausal women living in Taiwan. With the exception of increased body weight, no major side-effect was noted during this short-term study. [Taiwanese J Obstet Gynecol 2005;44(4):327-331]

Key Words: climacteric symptoms, menopausal treatment, STEAR, selective tissue estrogenic activity regulator, tibolone

Introduction

Tibolone is a new treatment with a unique pharmacologic profile licensed for the relief of climacteric symp-
metabolites. Each metabolite has different binding to the estrogenic, progestogenic, and androgenic receptors [3]. The 3-α and 3-β hydroxy metabolites exert estrogenic activity, but in a tissue-selective manner [3–12]. The δ-4 isomer shows both androgenic and progestogenic effects [2], which avoids stimulation of the endometrium [1,11]. Tibolone is easy to use: only a single tablet containing 2.5 mg tibolone is needed each day [8].

Climacteric symptoms sometimes bother perimenopausal women, resulting in severe interference in their quality of life, and HT is an effective method of relieving most climacteric symptoms. However, concerns have arisen regarding the possible association between breast cancer and HT. The largest meta-analysis to date, which included more than 90% of the literature [13], concluded that HT increases the risk of developing breast carcinoma and that this risk increases with the increasing duration of HT use. Once HT is stopped, this risk decreases, and it largely disappears by 5 years after cessation. Recent findings from the Women’s Health Initiative study show an increased incidence of invasive breast cancer during HT [14]. Although menopause is a natural event in women, some women suffer from symptoms that significantly affect their lives. Although circulating levels of estrogen are reduced in postmenopausal women, the breast tissue of postmenopausal women is able to synthesize estrogens locally, which explains why the risk of breast cancers is not minimized after menopause. In fact, estradiol is the main factor supporting the growth and evolution of breast cancers. One pathway involved in the transformation of estradiol is the sulfatase pathway, which transforms estrone sulfate to estradiol [9], especially after menopause. Tibolone and its metabolites are very potent inhibitors of the conversion of estrone sulfate to estradiol in the hormone-dependent breast cancer cell [9,10]. Tibolone metabolites regulate the activity of local enzymes normally involved in the production of active estrogens in the breast [12]. Tibolone has a different effect from conventional HT in the breast. It does not seem to stimulate breast tissue and might have an inhibitory effect on the growth of human breast tumor cells in vitro, and animal breast tumors [12], in addition to slowing down the proliferation rate and increasing differentiation and apoptosis [9]. In addition to the possibility of no increased risk of breast cancer, tibolone rarely causes breast tenderness and does not increase breast density [3,15]. Tibolone reportedly has a favorable tolerability profile [16]. Only a minority of women treated with tibolone experience vaginal bleeding, and the bleeding is mild and transient [4]. The advantageous tolerability/safety profile increases the acceptability of tibolone treatment and improves short- and long-term adherence to treatment [17]. However, these studies do not provide data about women living in Taiwan. Therefore, it is reasonable to evaluate the compliance with and efficacy of tibolone in symptomatic perimenopausal women in Taiwan.

**Methods**

Before initiation of the study, approval was granted by the independent ethics committee and institutional review board of the hospital. Women with a natural or surgically induced menopause who visited the hospital between September 2003 and June 2004 due to climacteric complaints were recruited into the study, whether they had received other HT or not. Once recruited, the case report form was immediately used to record baseline data, including basic demographic data, and the patient was scheduled for follow-up at the end of the third and sixth months of therapy with 2.5 mg tibolone daily. The case report form was used to record whether breast tenderness, insomnia, libido changes, mood swings, or bleeding episodes occurred during the study period. Weight was measured at the first visit and at the end of the sixth month for comparison.

**Results**

A total of 289 women in natural or surgical perimenopause were recruited into this study. Of these, 275 were still taking tibolone at the end of the study, which demonstrated a high retention rate (95.2%) (Figure 1). The rate of breast tenderness was significantly reduced from 26.5% at baseline to 2.8% at the end of the study. Only a minority of women treated with tibolone experience vaginal bleeding, and the bleeding is mild and transient [4].

![Figure 1](image_url)
The rate of insomnia decreased from 50.5% at baseline to 20.4% at the end of the study, and bleeding episodes decreased from 87.4% at baseline to 39.4% at the end of the study. The rate of mood instability was significantly reduced, from 84.1% at baseline to 44.3% at the end of the study. Libido (sexual satisfaction) significantly improved from 15.9% at baseline to 61.6% at the end of the study, which is a unique profile of tibolone due to the androgenic effect of its δ-isomer. Thirty women (10.4%) had improved vaginal dryness. Ten women (3.5%) developed an allergic reaction, three of whom dropped out of the study. One woman (0.3%) had breast tenderness and three (1%) complained of gastrointestinal disturbance. Three women (1%) had an attack of acne during therapy. Body weight changes in the women varied; most women (84.1%) had a weight increase ranging from 0.5 to 3 kg (Figure 2). Fourteen subjects dropped out for the following reasons: three for acne and/or an allergic reaction; four for intolerable weight gain and/or water retention; one due to headache and dizziness; and six for other personal reasons. During the 6-month evaluation period, seven women (2.4%) had been prescribed a half dose (1.25 mg) for personal reasons. No severe adverse events were reported during the observation period.

Discussion

Numerous clinical studies have shown that tibolone has beneficial effects in relation to climacteric symptoms and vaginal atrophy in postmenopausal women; relief from climacteric symptoms develops within 3–5 weeks, and the maximum effect is usually seen by 3 months [16]. In addition, tibolone shows beneficial effects on mood and sexual wellbeing [5–7,17]. The results of this study demonstrate a similar positive effect in improving insomnia, libido, and mood instability and, of most importance, there was a high rate of continuous use of tibolone. Moreover, a low dose (1.25 mg/day) also seemed to be effective. In this observational study, seven women were satisfied with this low-dose treatment, which is in agreement with a previous report showing that tibolone induced a decrease in the frequency and intensity of climacteric symptoms, leading to statistically significant differences compared to placebo, at doses of 1.25 mg and higher [18].

Concerning irregular vaginal spotting and/or possible unwanted pathologic changes to the endometrium, tibolone therapy is reported to have high rates of amenorrhea after 10 years, with minimal evidence of adverse effects on endometrial pathology [19]. In this study, we found that irregular bleeding episodes were markedly decreased both during and at the end of treatment.

In terms of biochemical changes in the blood, tibolone is reported to lower lipoprotein(a), fibrinogen, and plasminogen activator inhibitor-1 levels and to improve glucose tolerance, insulin sensitivity, and endothelial function. However, it also lowers high-density lipoprotein cholesterol by more than 20% [20]. Therefore, the long-term impact of tibolone on the risk of coronary heart disease is not known and needs to be studied [20]. We did not evaluate changes in blood biochemistry. However, significantly increased body weight was noted in this study, in disagreement with a previous report showing that tibolone is not associated with weight gain [15]. Due to the short-term follow-up,
we do not know the long-term effects of the increased body weight on these women taking tibolone, but we are highly concerned about these changes. We believe, therefore, that changes in body weight should be further studied and evaluated.

Tibolone, compared with conventional HT such as estrogen with or without progestogen, seems to be a relatively safe medication in terms of the risk of breast cancer. The Million Women Study Shows that the incidence of breast cancer is significantly increased in current users of preparations containing estrogen only (adjusted relative risk, 1.30 [95% confidence interval, 1.21–1.40]; \( p < 0.0001 \)), estrogen/progestogen (2.00 [1.88–2.12]; \( p < 0.0001 \)), and tibolone (1.45 [1.25–1.68]; \( p < 0.0001 \)), but the magnitude of the associated risk was substantially greater for estrogen/progestogen than for other types of HT (\( p < 0.0001 \)) [21–23]. An increase in mammographic density should be regarded as an unwanted side effect of HT [15]. In contrast to estrogen/progestogen treatment, tibolone seems to have little stimulating effect on breast tissue [15]. A recently published paper on the long-term effects of tibolone on mammographic density elaborates tibolone’s unique effects on the breast, and suggests that tibolone seems to have a minimal effect on mammographic density [3]. All of the above suggest that tibolone has an advantage over conventional HT in terms of breast cancer risk. Tamoxifen is often used as adjuvant therapy and/or preventive therapy for breast cancer. Unfortunately, many women with breast cancer suffer vasomotor symptoms rather than risk recurrence with conventional HT. In a small randomized controlled trial in women with early breast cancer undergoing adjuvant tamoxifen treatment, tibolone reduced hot flushes and night sweats and improved quality of life compared with placebo [24]. Moreover, tibolone prevents the increase in hot flushes in postmenopausal women given tamoxifen following surgery for breast cancer without untoward effects on the endometrium [25].

Tibolone prevents bone loss and increases bone mineral density in early and late postmenopausal women [4,8,26]. Since we did not evaluate bone mineral density during or at the end of tibolone treatment, we do not know the changes in bone mineral density in this short-term evaluation.

Some limitations of this study should be clarified. First, this is a relatively small study population, which may not provide strong evidence showing the true benefits of tibolone. Secondly, prescription behavior was not clearly identified within the scope of the measurement. Thirdly, increased body weight seems to be the major unwanted effect in this trial, and because of the small sample and dropouts, this issue should be re-evaluated in a future study. Fourthly, this is a descriptive study, and we did not use scientific statistics to analyze the data.

This study shows the efficacy of tibolone in insomnia, mood, and libido improvement, as well as its good tolerability (less breast tenderness and fewer bleeding episodes) in postmenopausal women.

References

Tibolone Compliance and Efficacy in Women Living in Taiwan


