Sequential tibolone versus progestin for premenopausal bleeding

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Abstract

Objective: *The aim of this study was to assess the impact of tibolone compared to dydrogesterone on endometrial thickness, breast density, quality of life and lipid profile status.* ***Method:*** *The double blind prospective-randomized study included forty-six perimenopausal women which were randomly assigned for treatment with either tibolone 2.5 mg/day (22 patients) or dydrogesterone 20 mg/day (24 patients) from day 14 to day 25 of the cycle, for 6 months. All women complained for climacteric symptoms and irregular menstrual cycle at least for the last six months.* ***Results:****During the 6 cycles of treatment, there was no significant difference between groups regarding the regularity of the cycles. Similarly, no significant difference was observed between groups regarding endometrial thickness, breast density, levels of estradiol, FSH, progesterone and lipid profiles. Regarding vertigo, mood disorder, depression, loss of libido, dryness of skin and vagina, tibolone therapy was found to be much more effective than progestin.*

Keywords: *tibolone, dydrogesterone, premenopausal bleeding*

Introduction

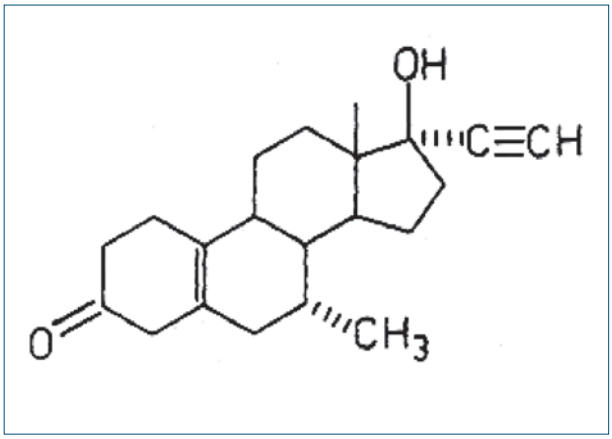
Tibolone, a member of the 19-nortestosterone family (Figure 1), is effective in the treatment of climacteric symptoms as hot flushes, sweat, mood and sleep disturbance, vaginal atrophy with dyspareunia and for the prevention of bone loss in postmenopausal women. It is metabolized into three different metabolites with varying degrees of estrogenic, progestogenic and androgenic activities. It mainly exerts estrogenic effects on vagina, bone, vasomotor symptoms - hotflushes, but it does not stimulate the endometrium (rather induces atrophy of the endometrium), suggesting that the drug itself has tissue-specific actions. The 3α-OH and 3ß–OH isomers mainly bind to the estrogen receptors, and the Δ4 isomer, formed locally in the endometrium by 3 ß - hydroxysteroid dehydrogenase/isomerase, preferentially binds to progesterone and androgen receptors and is responsible for the atrophy-inducing effects in the endometrium[1].

Progesterone and some progestins exert powerful antiestrogen effects when administered in pharmacologic doses. Progestins diminish estrogen effects on target cells by inhibiting the augmentation of estrogen receptors that ordinarily accompanies estrogen action (receptor replenishment inhibition). This influence account for the antimitotic, antigrowth impact of progestins on the endometrium, prevention and reversion of hyperplasia, limitation of growth postovulation and development of marked atrophy[2].

In premenopausal patients, the relative hyperestrogenemia and hypoprogesteronemia induces irregular cycles, with arrheomenorrhea or in contrast hypermenorrhea. In the majority of patients the instable menstrual cycles coexist with lots of uncomfortable symptoms. The classical therapeutic option is to give progestins for 10 to 14 days per month (cycle), beginning from the day 14 or 15 to day 24 or 25 of the cycle to balance the relative hyperestrogenemia of the second phase and to induce an artificial but regular menstrual bleeding a few days after the progestin is stopped. This therapeutic schema makes a 27-30 days cycle, decrease the premenstrual symptoms and protect the endometrium to turn in hyperplasia.

The objective of this blind prospective-randomized work was to study, in premenopausal patients with irre-

Figure 1. Tibolone`s structure



gular cycles, the impact of tibolone, administered sequentially, on endometrial thickness, breast density, quality of life and lipid profile status, in comparison with a similar group of patients with the same symptomatology treated with a progestin chemically close to the natural progesterone: dydrogesterone.

Materials and Methods

This is a prospective, randomized, controlled study. Fifty-eight perimenopausal women were randomly allocated to treatment with either tibolone 2.5 mg/day or Duphaston 20 mg/day from day 14 to day 25 of the cycle (12 days), for 6 months. Informed consent, approved by the Institutional Review Board, was obtained from study participants. Women were similar with respect to demographic characteristics and age (range 40-46 years).

All women complained for climacteric symptomatology and irregularity in menstrual cycle periodicity (spaniomenorrhea and polymenorrhea) at least for the last six months. Exclusion criteria for the enrolment were the administration of short-acting hormones/contraceptive regiments 3-months prior the initiation of the study, history of hysterectomy, existence of hormone-dependent neoplasms, vaginal bleeding of unknown etiology, serious hepatic disorders, cardiovascular and coagulation disorders. Twelve patients were excluded because they stopped treatment before the end of the study or stopped because of side effects.

After enrolment, 22 patients (group T) were randomized to receive tibolone 2.5 mg/day for 12 days per month during the 6-month study period (1 tablet Livial 2.5 mg per day from day 14 to day 25). The remaining 24 patients (group D) received dydrogesterone 20 mg/ day for 12 days per month during the 6-month study period (=2 tablets Duphaston 10 mg per day from day 14 to 25). All patients were instructed to notice the regularity of their menstruation and to answer a modified ``Kupperman Index``, which is a method index rating the severity of climacteric symptoms3. The following symptoms were determined, with the weighted factor per symptom in brackets: hot flushes4, sweating (2), paresthesias (2), insomnia (2), vaginal dryness (l), dysphoria (l), heart's palpitations (l), headache (l), nervousness (l), vertigo (l), mood disorder (l) and depression (1), significant decrease of libido (1), skin's dryness (l) and muscle-joint-bone ache (1). The evaluation grades of the climacteric symptoms were: no complaints (score: 0), mild complaints (score: l), moderate complaints (score: 2) and severe complaints (score: 3).

In addition, endometrial thickness was measured sonographically with intravaginal probe at each follow-up examination. Endometrial thickness was measured on day 3 or 4 of the cycle, with a midline sagittal image of the uterus as a summation of the anteroposterior width of both the anterior and posterior endometrial layers, exclusive of possible intracavitary content (taking into account that during the normal menstrual cycle, the endometrium becomes progressively thicker and more echogenic and the endometrial thickness, may reach up to 10 mm-or more in the secretory phase).

Breast density was evaluated by mammography (face and profile) at the end of the survey and compared to a previous mammography not older than 12 months. Breast mammographic density was classified as: 0% ("fatty breasts"), less than 25%, more than 25%-less than 50% (the most common situation in women over 50 years old), more than 50%-less than 75% (more common in younger women) and more than 75% ("dense breasts"). Any suspicious findings were classified according to ACR (American Cancer Radiology) classification as follows:

Category 0: Need additional imaging evaluation;
Category 1: Negative;
Category 2: Benign finding;
Category 3: Probably benign finding? Short interval follow-up suggested;
Category 4: Suspicious abnormality? Biopsy should be considered;
Category 5: Highly suggestive of malignancy? Appropriate action should be undertaken.

Blood samples were obtained for estradiol and FSH levels on 3rd or 4th day of the cycle and for progesterone on day 20th or 21st in both groups. Blood samples were also obtained in both groups for glucose, triglyceride, HDL and LDL cholesterol levels, coagulation and liver function tests. Considering as normal levels of LDL cholesterol, values lower than 130 mg/dL, LDL cholesterol was higher than normal in 5 patients of group T (135-148 mg/dL) and in 4 patients of group D (134-160 mg/dL). Considering as normal levels of triglycerides (for ages 40-49), values of 66-139 mg/dL, triglycerides were higher than normal in 3 patients of group T (157-172 mg/dL) and in 4 patients of group D (154-185 mg/dL) and glucose was higher than 100 mg/dL in one patient of group T and in one of group D. Liver enzymes were normal in all patients. Lab values are shown in Table I for both groups.

Results

Regarding the regularity of the cycles (considering as regular 27-31 days of intermenstrual interval), the following patterns were recorded during the 6 cycles of treatment:

In group T (22 women), fifteen patients (68,2%) had 6 regular cycles, four patients (18,2%) had 4 regular cycles,

Table 1 Baseline Lab values-mean±standard deviation (range) in mg/dL for both groups. T=Tibolone group, D=Dydrogesterone group.

	Tibolone N=22	Dydrogesterone N=24	Statistic significance
Triglycerides	116/29.6 (66-172)	109.3±33.1 (67-185)	**NS**
Cholesterol	204.6±22.1 (132-240)	205±19.1 (170-247)	**NS**
HDL	60.6±8.6 (48-82)	59.7±8.8 (49-78)	**NS**
LDL	99±28.8 (60-148)	95.7±30.8 (58-160)	**NS**
AST	23.1±6.7 (11-37)	25±9.6 (10-40)	**NS**
ALT	25.9±8 (14-42)	28.7±10.7 (8-48)	**NS**

two patients (9,1%) had 2 regular cycles and one patient (4,5%) had only one regular cycle (Figure 2).

In group D (24 women), sixteen patients (66,7%) had 6 regulars cycles, two patients (8,3%) had 4 regular cycles, two patients (8,3%) had 2 regular cycles and four patients (16,6%) had only one regular cycle (Figure 3). Comparing these results to those of group T, there was no statistical difference (p>0.1).

The endometrium remained atrophic (<5 mm) on day 3 or 4 in 19 (86%) of 22 patients of group T and 23 (96%) of 24 patients of group D (p>0.1). Two women (9%) of group T and one woman of Group D (4%) reported intermenstrual bleeding after three months of therapy (p>0.1).

Regarding breast density, in group T, this was unchanged in 19 cases (86%), showed slight increase in 3 cases (14%) and moderate increase in 1 case (4,5%). In group D, breast density was unchanged in 23 cases (96%) and showed slight increase in 1 case (4%). As a total, there was no statistical difference between groups regarding breast density.

Mean levels of estradiol, FSH and progesterone were 52, 21 and 2.6 respectively for group T and 49, 18 and 3.4 respectively for group D (p>0.1).

Regarding the climacteric symptoms the following results must be noted: Modified Kupperman Index of the T and D groups was 30.4± 6.5 (mean +-SD) and 31.5 ± 7.1 respectively at the start and 24.2±5.0 and 29.4±6.8 respectively at the end of the study (p>0.05). Regarding vertigo, mood disorder, depression, loss of libido, dryness of skin and vagina, tibolone therapy was found to be much more effective than progestin. Actually, 17, 13, 10, 14 and 16 patients of group T reported improvement of vertigo, depression, mood disorder, loss of libido, dryness of skin and vagina respectively, versus 8, 5, 4, 6 and 7 respectively in group D, with p<0.05 in all symptoms (Figure 4).

Regarding lipid profiles, after six months of treatment, there was no statistical change in both groups, although HDL levels were substantially higher in T group (65.5 mg/dL).

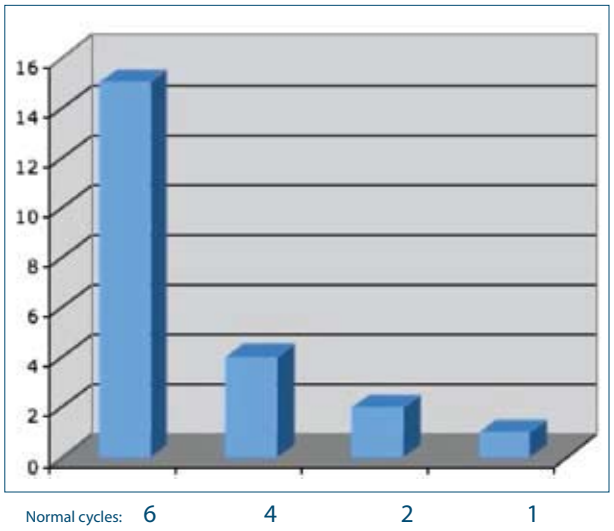


Figure 2. Number of patients (vertical axis) and number of normal cycles per patient (horizontal axis) in tibolone group

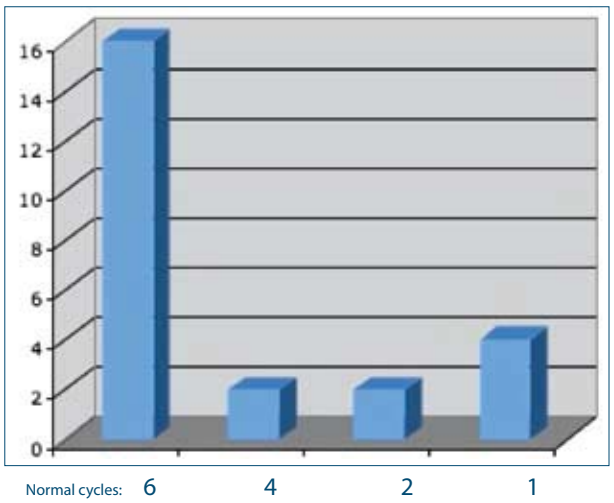


Figure 3. Number of patients (vertical axis) and number of normal cycles per patient (horizontal axis) in dydrogesterone group

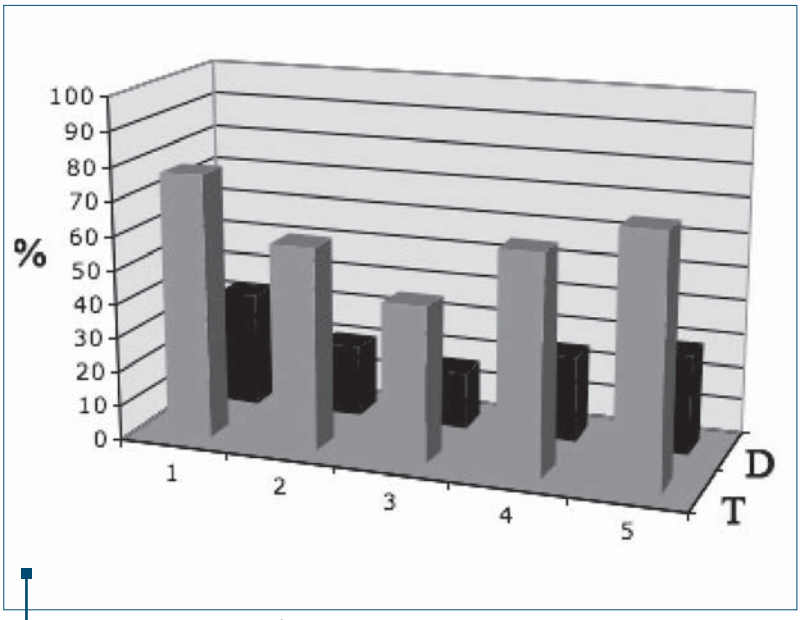


Figure 4. Percentages of symptoms improvement in both groups (T=tibolone group, D= dydrogesterone group, 1=vertigo, 2=depression, 3=mood disorder, 4=loss of libido, 5=dryness)

Discussion

As observed and in our study, in recent studies dydrogesterone (combined with 17beta-oestradiol) provided excellent endometrial safety and was associated with an acceptable bleeding profile[4]. Similarly, our results showed that tibolone "regulated" menstrual cycles and caused significant less vaginal bleeding as it was observed and in other trials-compared to conventional low-dose combined hormone therapy[5].

Although tibolone was given for fewer days in our study (half total dose per month than the classical protocol), it conserved its activity in sexual dysfunction6, and it seems that its androgenic activity is maintained even in smaller doses. It must also be noted that although tibolone was accused for lowering HDL in its original administration[7], our study showed in contrast increased HDL in its sequential administration.

Tibolone is originally designed for continued administration in menopause. However, the progestogenic activity of its metabolites8 could justify its sequential administration, as other progestogens given in perimenopausal women. Actually, in our study, it was shown that tibolone, given sequentially, can both regulate the cycle and improve climacteric symptoms. Taking into account the progestogenic effect of tibolone, our study shows that this regimen could probably be given sequentially in climacteric women. Although, it is well known that progestogens could have important benefit results in the premenopausal climacteric, including bleeding disorders9, their action on serious climacteric symptomatology is minimal. Previous trials showed climacteric symptoms improvement in women taking medroxyprogesterone acetate as monotherapy[10], and some benefit in mild psychosomatic symptoms[11], however, this kind of therapy is seldom prescribed for severe climacteric symptoms relief. On the other hand, tibolone proved effective in highly symptomatic climacteric women[12] and those with several psychosomatic symptoms[13] and its effectiveness was tried in different doses, including those that are lower of the usual daily administration[12]. Similarly, in our study tibolone was actually administered in a total month dose that is lower than the "usual" one and it proved effective.

Conclusion

In this pilot study "sequential tibolone" decreased climacteric complaint more effectively than dydrogesterone and similarly regulated cycles without irregular spotting or harmful side effects. Tibolone could be a good option in premenopausal patients with irregular cycles and climacteric symptoms, taking into account the safety of its action on endometrium with a low prevalence of endometrial hyperplasia (<0.2%), no endometrial carcinoma[14] and good metabolic profile. Moreover, no significant increase of breast density was found, which suggest the (probable) safety of sequential Tibolone on breast.

This study suggests that Tibolone, given sequentially in premenopausal women, is a good and safe alternative to progestin therapy. Further studies, with more cases, could confirm our results. ■

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