

Efficacy and safety of oral tibolone 1.25 or 2.5 mg/day vs. placebo in postmenopausal women

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Abstract. – **Background:** tibolone at usual doses of 2.5 mg/day in postmenopausal women has been shown to improve climacteric complaints, without affecting endometrial thickness and lipid profile or blood glucose. However, the potentially similar efficacy, but better tolerability, of a low dose of this drug (1.25 mg) has never been established.

Methods: 162 healthy, non-obese, postmenopausal women, aged 40-65 years, with an intact uterus were enrolled in a national, single centre, randomised, double blind, placebo controlled, parallel group trial. After 1 week of run-in, patients were treated for 24 weeks with placebo, tibolone 1.25 mg or 2.5 mg/day. During the study laboratory tests, endometrial ultrasound scans and mammography were performed. Occurrence of menopausal signs and symptoms, including vaginal bleeding, and quality of sexual life were also checked.

Results: in the 120 patients terminating the study without major protocol violations, climacteric symptoms were similarly improved by tibolone 1.25 and 2.5 mg (78% and 90% reduction at week 24 for hot flushes, 36% and 34% for sweating episodes and 44% and 51% for vaginal dryness), but not by placebo. Benefits occurred earlier in the group treated with tibolone 2.5 mg. Quality of sexual life was almost invariably improved by tibolone as compared to placebo, but improvement occurred earlier in the tibolone 1.25 mg group. Severity of vaginal bleeding was not different between placebo and active treatment groups, except at week 12 when was higher. At the end of treatment vaginal bleeding occurred in 15% of patients treated with placebo, 14% treated with tibolone 1.25 mg and 12% treated with tibolone 2.5 mg. Endometrial thickness and breast density were not changed by treatment, as well as FSH, 17- β -estradiol, total cholesterol, HDL and LDL cholesterol, triglycerides and blood glucose. Adverse events were reported by 14.7%, 26.7% and 24.4% of patients treated with placebo, tibolone 1.25 mg and tibolone 2.5 mg/day, respectively.

Conclusions: tibolone at doses of 1.25 or 2.5 mg/day given for 24 weeks to postmenopausal women displayed similar efficacy and safety profiles, though were more effective than placebo. Tibolone 1.25 mg induced a more gradual relief from climacteric symptoms and a more prompt improvement of sexual function.

Key Words:

Postmenopausal, Climacteric symptoms, Sexual life, Vaginal bleeding, Lipid profile, Tibolone.

Introduction

Menopause is frequently characterized by occurrence of vasomotor symptoms (hot flushes, nausea, dizziness, headache, palpitations, night sweat, etc.), alteration of sexual function and changes in lipid profiles^{1,2}. Vasomotor symptoms, and in particular hot flushes, may negatively affect patient's quality of life³, while the increase in total cholesterol and triglycerides may be responsible for an increased risk of coronary heart disease⁴. Several controlled clinical trials have shown that the most effective form of therapy for vasomotor symptoms is estrogen replacement therapy or hormone replacement therapy (estrogens combined with progestin)⁵. This treatment also affects lipid metabolism, by increasing high density lipoprotein cholesterol (HDL) and triglycerides and by reducing total and low dose lipoprotein (LDL) cholesterol, the increase in triglycerides being potentially not beneficial for the cardiovascular system⁶⁻⁸.

Tibolone is a synthetic pro-drug steroid that has several different metabolites with tis-

sue-specific estrogenic, progestogenic and androgenic properties^{9,10}. In post-menopausal women, tibolone at doses of 2.5 mg/day has been shown to improve climacteric complaints (in particular vasomotor symptoms and vaginal lubrication) and libido¹¹⁻¹⁵, to prevent osteoporosis^{11,16-19} and to improve some lipid parameters, without affecting endometrial thickness and uterine fibroids volume^{11,14,20-25}. In particular, its androgenic action may reduce triglycerides, though unfortunately also HDL cholesterol, both commonly increased by estrogens^{11,26}. The main unwanted effect of tibolone is vaginal bleeding, which, however, is reported in half as many cases as respect to estrogens²⁷⁻²⁹.

Aim of the present study was to assess the efficacy, in terms of control of symptoms and improvement of sexual function, the safety and the effects on lipid profile and blood glucose, of a low dose of tibolone (1.25 mg) vs. the usually employed dose (2.5 mg) and vs. placebo. The study hypothesis was that a low dose of tibolone might have been more effective than placebo and as effective as a 2.5 mg dose, but safer.

Material and Methods

Study Population

The study included 162 healthy, non-obese, postmenopausal women, aged between 40 and 65 years, with an intact uterus. Menopause was defined by the evidence of at least 12 months of amenorrhea with levels of FSH > 30 mIU/ml and of 17- β -estradiol < 50 pg/ml. Patients were excluded if they had: (1) previous deep thrombophlebitis or cerebral apoplexia; (2) mammary or gynaecological neoplasia; (3) uncontrolled diabetes; (4) abnormal mammography; (5) abnormal values of C-reactive and S-coagulative protein; (6) endometrial thickness > 4 mm or an abnormal Papanicolaou smear; (7) abnormal bleeding of undetermined origin; (8) history of hepatic or renal diseases; (9) use of estrogenic, progestinic or androgenic drugs in the 8 weeks preceding enrolment into the study; (10) use of IUD in the preceding 3 months; (11) use of medications known to affect vasomotor system in the 2 weeks prior to enrolment; (12) known hypersensitivity to study

drugs; (13) glucose intolerance (blood glucose > 125 mg/dl), hypercholesterolemia (total cholesterol > 300 mg/dl) or hypertriglyceridemia (triglycerides > 300 mg/dl), hypertension (systolic blood pressure > 160 mm Hg or diastolic blood pressure > 90 mm Hg).

Written informed consent was obtained from all patients prior to their inclusion into the study, which was approved by the Ethics Committees of the centres involved.

Study Design

This was a national (Romania), single centre, randomised, double blind, placebo controlled, parallel group trial consisting of a 1 week run-in followed by a 24 week treatment period with placebo, tibolone 1.25 mg or tibolone 2.5 mg given orally and once daily with a 1:1:1 ratio.

Medical history was collected and a physical examination (including gynaecological examination), laboratory tests (FSH and 17- β -estradiol determination, blood glucose, total cholesterol, LDL and HDL cholesterol and triglycerides), ultrasound scan (for assessment of endometrial thickness) and mammography were performed at inclusion (visit 1). Laboratory tests, ultrasound scan and mammography were repeated at the end of the study. At the time of randomization (visit 2) and after 4, 12 and 24 weeks of treatment (visit 3, 4 and 5, respectively) occurrence of clinical signs and symptoms (hot flushes, sweating episodes, vaginal dryness and vaginal bleeding) was checked, and severity was quantified using a five-point scoring system (0 = none, 1 = light, 2 = moderate, 3 = severe, 4 = very severe). Sexual activity was assessed and quantified using an adapted version of McCoy sex scale questionnaire based on a five-point scoring system³⁰. Occurrence of adverse events was recorded at visit 3, 4 and 5.

Data Analysis

Main study objective was to demonstrate the equivalence of tibolone 1.25 mg and 2.5 mg and their superiority as compared to placebo in reducing the severity of menopausal symptoms (hot flushes, sweating episodes and vaginal dryness). Starting from this assumption sample size estimation by a two-sided test ($\alpha = 0.05$, power = 80%) indicated that at least 162 pa-

tients (54 patients for each treatment group) had to be randomised in order to have 120 valuable subjects.

The primary efficacy end-point of the study was the severity of menopausal symptoms in the three treatment groups at baseline and after 4, 12 and 24 weeks of treatment. Secondary end-points were among treatments comparisons of: (1) severity of vaginal bleeding at week 0, 4, 12 and 24; (2) quality of sexual life at week 0, 4, 12 and 24; (3) laboratory parameters (total plasma cholesterol, LDL and HDL cholesterol, triglycerides and blood glucose) at week -1 and 24; and (4) results of ultrasound scan and mammography at week 0 and 24. Percentage of patients reporting climacteric symptoms, improvement of sexual life or vaginal bleeding was also calculated for each study visit.

The analysis was carried out on patients with all valid efficacy variables and who terminated the study without major protocol violations (per-protocol analysis). Among treatments comparison of primary variables was made by analysis of variance with contrasts, separately performed for each time point of the study. Analysis of vaginal bleeding and quality of sexual life was carried out as the primary analysis. Results of laboratory tests performed before and at the end of treatment were compared by analysis of variance, taking into account the interaction between time (visits) and treatment group.

Safety assessment was based on recording of the occurrence of adverse events and on analysis of laboratory data, vital signs and physical examination outcomes. Adverse

events were summarised by treatment group and by type of event.

Homogeneity of demographic, clinical and laboratory data at baseline was verified by analysis of variance for continuous variables and by a Chi-square test for categorical variables.

Data are shown as means \pm SD. A $p < 0.05$ was used as the level of statistical significance.

Results

Demographic and Clinical Data

A total of 162 patients were randomised to treatment and took at least one dose of study drugs. Of these, 42 discontinued the study because of adverse events, lost to follow-up, consent withdrawal, lack of efficacy or other minor problems. Thus, the patients valid for analysis were 120, of whom 34 randomised to placebo, 45 to tibolone 1.25 mg and 41 to tibolone 2.5 mg.

Before treatment the three groups were similar for age, sex distribution, height, weight, menopause interval, rate of births and abortions (Table I). Also results of hormonal and biochemical laboratory tests were comparable across treatment groups (Table I and II).

Climacteric Symptoms and Sexual Activity

All 120 patients reported hot flushes, sweating episodes and vaginal dryness at randomisation, the average severity score

Table I. Demographic, clinical and laboratory data of the study population before randomization to treatment (means \pm SD). Data are shown for patients terminating the study without major protocol violations ($n = 120$).

| | Placebo ($n = 34$) | Tibolone 1.25 mg ($n = 45$) | Tibolone 2.5 mg ($n = 41$) |
|----------------------------|-------------------------|----------------------------------|---------------------------------|
| Age (years) | 56 \pm 5 | 54 \pm 5 | 56 \pm 5 |
| Height (cm) | 163 \pm 4 | 161 \pm 5 | 163 \pm 4 |
| Weight (kg) | 66 \pm 6 | 65 \pm 7 | 68 \pm 6 |
| Menopause interval (years) | 3 \pm 2 | 3 \pm 2 | 4 \pm 2 |
| Births (%) | 88 | 93 | 93 |
| Abortions (%) | 82 | 87 | 85 |
| Total cholesterol (mg/dl) | 209 \pm 15 | 211 \pm 13 | 214 \pm 20 |
| HDL-cholesterol (mg/dl) | 58 \pm 3 | 57 \pm 4 | 58 \pm 4 |
| LDL-cholesterol (mg/dl) | 152 \pm 15 | 154 \pm 13 | 156 \pm 20 |
| Triglycerides (mg/dl) | 183 \pm 61 | 195 \pm 61 | 200 \pm 68 |
| Blood glucose (mg/dl) | 99 \pm 14 | 94 \pm 12 | 96 \pm 9 |

Table II. Results of hormonal tests at baseline and at the end of treatment (means \pm SD). Data are shown for patients terminating the study without major protocol violations (n = 120).

| | Placebo (n = 34) | Tibolone 1.25 mg (n = 45) | Tibolone 2.5 mg (n = 41) |
|--|---------------------|------------------------------|-----------------------------|
| FSH (mIU/ml) | | | |
| Baseline | 44 \pm 10 | 43 \pm 7 | 42 \pm 10 |
| 24 weeks | 44 \pm 9 | 44 \pm 7 | 43 \pm 10 |
| 17-β-estradiol (pg/ml) | | | |
| Baseline | 40 \pm 3 | 39 \pm 3 | 40 \pm 4 |
| 24 weeks | 42 \pm 5 | 41 \pm 5 | 41 \pm 5 |

being comparable across treatment groups (Figure 1). During treatment the average score was progressively and significantly ($p < 0.01$) reduced by active treatment, but not by placebo. Benefit on climacteric symptoms occurred earlier in the group treated with tibolone 2.5 mg than in that treated with the 1.25 mg dose ($p < 0.01$ at 4 weeks for hot flushes and sweating, $p < 0.05$ at 12 weeks for sweating only). Effect on vaginal dryness was prompt and similar between the two active treatment groups (Figure 1). At the end of treatment (24 weeks) the percent reduction from baseline in the number of patients reporting hot flushes in the tibolone 1.25 and 2.5 mg was 78% and 90% respectively, for sweating episodes was 36% and 34% and for vaginal dryness was 44% and 51%. All patients under placebo still reported climacteric symptoms at the final evaluation.

Quality of sexual life was almost invariably improved by tibolone as compared to placebo, with a mean score significantly higher under 1.25 mg than under 2.5 mg at 12 weeks, the opposite being observed after 24 weeks of treatment. Rate of patients reporting at least an acceptable quality of sexual life increased from 56% (baseline) to 82% (24 weeks) in the placebo group, from 51 to 96% in the tibolone 1.25 group and from 37% to 100% in the tibolone 2.5 mg group (Figure 2).

Severity of vaginal bleeding was not significantly different between the active treatment group and under placebo, except at week 12. No between-groups difference was observed for tibolone 1.25 mg and 2.5 mg at any study time point. At the end of treatment (week 24), the incidence of vaginal bleeding was similar in the three treatment group (15% in

the placebo group, 14% in the tibolone 1.25 mg group and 12% in the tibolone 2.5 mg group).

Ultrasound Scan and Mammography

Ultrasound scans performed at study inclusion and at the end of the 24 weeks of treatment did not show any significant increase in endometrial thickness in any study group (data not shown). No increase of breast density was observed after 24 weeks of treatment in the three randomisation groups (in three patients randomised to tibolone 1.25 mg a reduction of breast density was observed).

Hormonal and Biochemical Parameters

As shown in Table II, FSH and 17- β -estradiol levels were unchanged at the end of treatment, no significant differences being observed among the three treatment groups. Also total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides and blood glucose did not significantly change during treatment (data not shown).

Safety

Safety analysis was carried out in all the 120 patients of the main study analysis. A total of 27 (22.5%) patients reported at least one adverse event, 5 were randomised to placebo, 12 to tibolone 1.25 mg and 10 to tibolone 2.5 mg. Type and distribution of adverse events are reported in Table III.

Discussion

The present study aimed at assessing the efficacy and safety of a low dose of tibolone

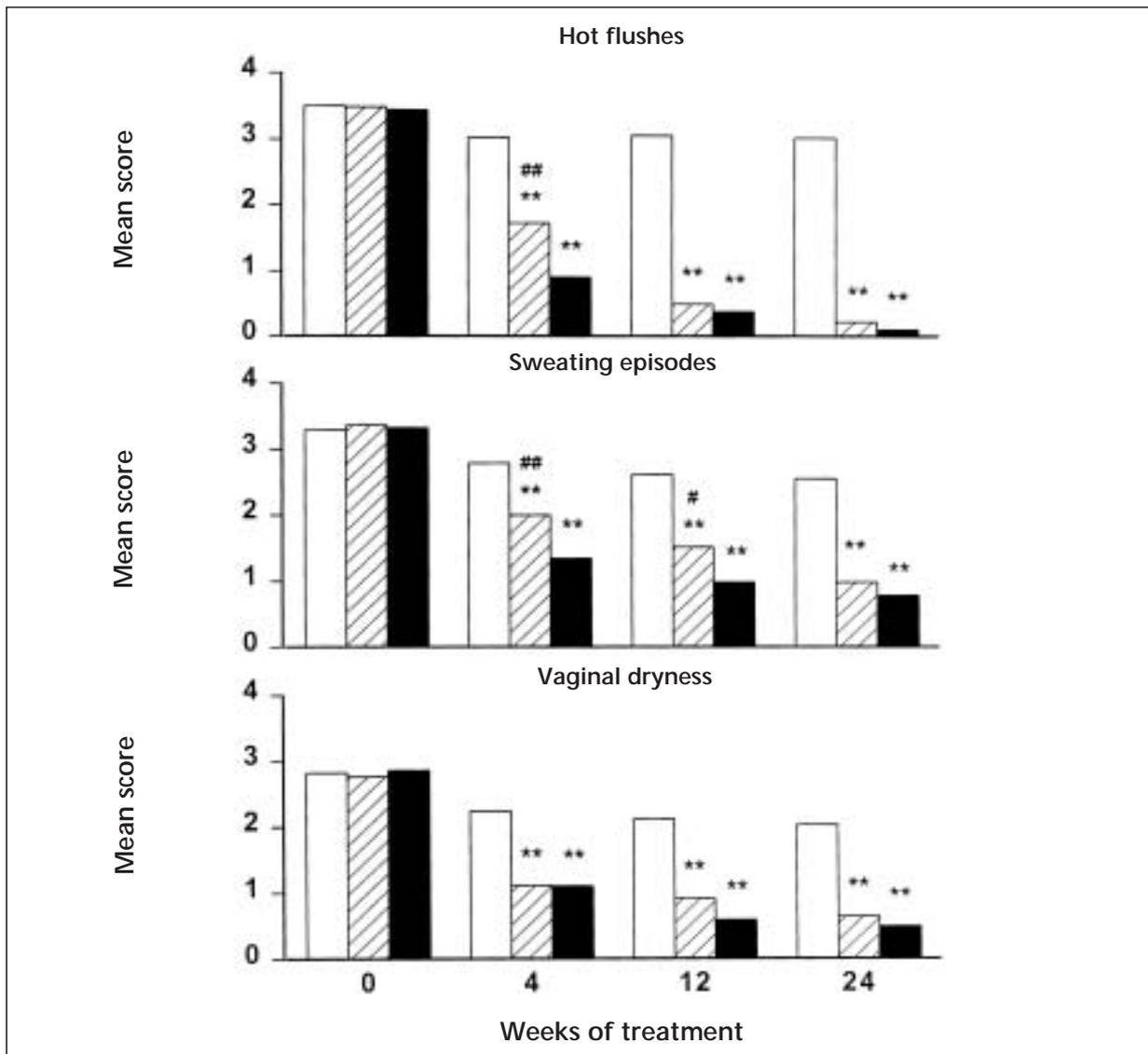


Figure 1. Mean scores for climacteric symptoms (hot flushes, sweating episodes and vaginal dryness) at randomisation and after 4, 12 and 24 weeks of treatment. Data are shown for the placebo (n = 34, open bars), tibolone 1.25 mg (n = 45, striped bars) and tibolone 2.5 mg (n = 41, full bars) treatment groups. Asterisks identify statistically significant differences between tibolone and placebo (** $p < 0.01$) while # refer to statistically significant difference between tibolone 1.25 and 2.5 mg (# $p < 0.05$, ## $p < 0.01$).

(1.25 mg) vs. the usually employed dose (2.5 mg) and vs. placebo, assuming that a low dose of tibolone might have been as effective as a 2.5 mg dose, but safer, and more effective than placebo. Results of the analysis of the various study endpoints are extensively discussed in the following paragraphs.

Concerning the efficacy of tibolone on climacteric complaints (hot flushes, sweating and vaginal dryness), our study showed that

tibolone 1.25 and 2.5 mg have a greater effect than placebo, both in terms of reduction of overall score and of the number of patients reporting symptoms. Patients with hot flushes were reduced by 78% and 90% (tibolone 1.25 and 2.5 mg respectively), those reporting sweating by 36% and 34% and those with vaginal dryness by 44% and 51% after 24 weeks. These reductions were similar or even larger than those observed in other random-

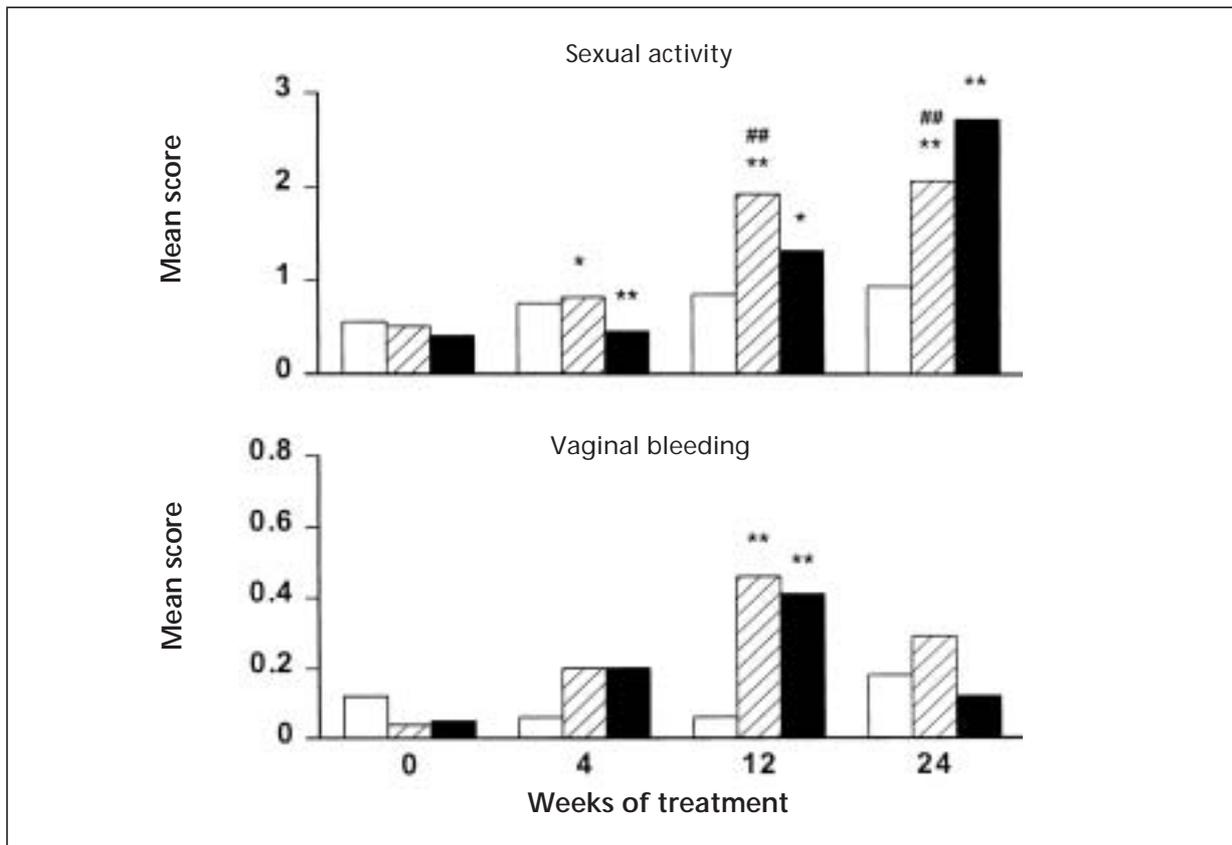


Figure 2. Mean scores for quality of sexual activity and vaginal bleeding at randomisation and after 4, 12 and 24 weeks of treatment. Data are shown for the placebo ($n = 34$, open bars), tibolone 1.25 mg ($n = 45$, striped bars) and tibolone 2.5 mg ($n = 41$, full bars) treatment groups. Asterisks identify statistically significant differences between tibolone and placebo (** $p < 0.01$, * $p < 0.05$) while # refer to statistically significant difference between tibolone 1.25 and 2.5 mg (## $p < 0.01$).

ized trials making use of tibolone and sharing a similar study design and sample size¹²⁻¹⁴. They were also similar to those achieved with hormonal replacement therapy^{28,31}.

A recent study assessing the pharmacokinetic of tibolone has shown that 2.5 mg and

1.25 mg tablets are bioequivalent with respect to the extent of absorption³². In our study we demonstrated for the first time that in spite of a similar pharmacokinetic, the clinical effect of tibolone 2.5 mg dose occurred earlier than that of the 1.25 mg dose. As a matter of fact

Table III. Patients reporting adverse events during the course of the study in the three randomization groups.

| | Placebo ($n = 34$) n (%) | Tibolone 1.25 mg ($n = 45$) n (%) | Tibolone 2.5 mg ($n = 41$) n (%) |
|-------------------|------------------------------------|---|--|
| Breast discomfort | – | 2 (4.4) | 4 (9.7) |
| Fluid retention | – | 3 (6.7) | 2 (4.9) |
| Vaginal spotting | 2 (5.9) | 4 (8.9) | 2 (4.9) |
| Headache | 2 (5.9) | 3 (6.7) | 2 (4.9) |
| Nausea | 1 (2.9) | – | – |
| <i>Total</i> | 5 (14.7) | 12 (26.7) | 10 (24.4) |

overall severity and rate of patients reporting hot flushes were lower after 4 weeks in the tibolone 2.5 mg than in the 1.25 mg group, and sweating episodes were less severe and frequent in the tibolone 2.5 mg than in the tibolone 1.25 mg group both at 4 and 12 weeks. However, at the end of the study (24 weeks) the two doses were comparable as respect to their efficacy on climacteric symptoms. The less prompt effect on vasomotor symptoms of tibolone 1.25 mg as respect to tibolone 2.5 mg, may support the use of the lower dose of the drug in those patients in whom a gradual, instead of a brisk and more consistent relief of climacteric symptoms, is recommendable, for instance for safety reasons.

Tibolone has been shown to increase libido and frequency of sexual activities, most likely due to its androgenic activity¹⁵ and to a greater extent than hormone replacement therapy³³. In our study, we observed a sensible improvement in sexual function with tibolone. However, a more rapid improvement in quality of sexual life was reached in the tibolone 1.25 mg group, while in the tibolone 2.5 mg group the improvement was smoother and at the end of the study was greater than that reported with tibolone 1.25 mg dose. As discussed for climacteric symptoms, this result seems to indicate that use of tibolone 1.25 mg should be restricted to those patients in whom a rapid instead of a consistent improvement in quality of sexual life has to be achieved.

Vaginal bleeding or spotting have been reported in 10-20% of patients treated with tibolone, mainly during the first 4-6 months of treatment and particularly in younger women, those undergoing a natural menopause or using the drug within 12 months of their last menstrual period. In previous randomized clinical trials, treatment with tibolone caused significantly more vaginal bleeding than placebo²⁷, but about half as much as estrogens^{28,29}. Also in our study vaginal bleeding occurred more frequently in the active treatment than in the placebo group, but a significant difference was evident only at week 12, while at the end of the study the overall score and the rate of patients reporting this peculiar adverse event was similar in the three randomization groups. The positive finding of the present study is that the incidence of vaginal bleeding observed at the end

of treatment under placebo (15%) or tibolone (12% with 2.5 mg and 14% with 1.25 mg) was similar or much less than that seen in previous randomized studies (25% to 12% under tibolone 2.5 mg and 14% under placebo)²⁷⁻²⁹. The absence of a significant vaginal bleeding under tibolone was also confirmed by the fact that endometrial thickness, as determined by ultrasound scan was unchanged at the end of treatment in all the three randomisation groups. Also breast tissues were not augmented, a finding confirming the lack of a significant trophic activity of tibolone as respect to placebo.

In postmenopausal women there is typically an increase in total cholesterol and triglycerides, mostly due to an increase in LDL cholesterol, whereas HDL cholesterol remains unchanged. Compared to placebo tibolone reduces HDL^{14,20-24} and triglycerides^{14,21-23}, has no effect¹⁴ or reduces total cholesterol²², and does not affect LDL cholesterol^{20,23}. These effects on lipid metabolism distinguish tibolone from estrogens which decrease LDL cholesterol and increase HDL cholesterol and triglycerides^{25,26}. In our study, the lipid profile, and in particular blood cholesterol, a well recognized cardiovascular risk factor, was not adversely affected by treatment with tibolone³⁴.

Recently, an open label study compared the effects of tibolone 2.5 mg vs. conjugated equine estrogens and medroxyprogesterone over 24 weeks in 27 postmenopausal women³⁵, showing no clinically relevant effects on carbohydrate metabolism with both drugs. Another study³⁶ conducted in 22 healthy postmenopausal women over 12 weeks showed no negative effects of tibolone on glucose metabolism. Also in our study blood glucose was not affected by treatment with either tibolone 1.25 mg or tibolone 2.5 mg, thus confirming the metabolic neutrality of this synthetic steroid as respect to this parameter.

In conclusion, our study showed that tibolone at a dose of 1.25 or 2.5 mg given to postmenopausal women is effective in improving climacteric symptoms and quality of sexual life, as compared to placebo. In terms of safety, no negative effects were observed on lipid and glucose metabolism, while incidence of vaginal bleeding was comparable to that observed in other studies on tibolone.

Thus, though tibolone 1.25 and 2.5 mg share a comparable safety profile, the 1.25 mg dose seems to be of advantage when a more gradual relief from symptoms and a more prompt improvement of sexual function is requested in postmenopausal women.

References

- 1) DENNERSTEIN L, DUDLEY EC, HOPPER JL, GUTHRIE JR, BURGER HG. A prospective population-based study of menopausal symptoms. *Obstet Gynecol* 2000; 96: 351-358.
- 2) DE ALOYSIO D, GAMBACCIANI M, MESCHIA M, et al. The effect of menopause on blood lipid and lipoprotein levels. The Icarus Study Group. *Atherosclerosis* 1999; 147: 147-153.
- 3) DALY E, GRAY A, BARLOW D, MCPHERSON K, ROCHE M, VESSEY M. Measuring the impact of menopausal symptoms on quality of life. *Br Med J* 1993; 307: 836-840.
- 4) KNOPP RH. Risk factors for coronary artery disease in women. *Am J Cardiol* 2002; 89 (suppl.12): 28E-34E.
- 5) RYMER J, MORRIS EP. Extracts from "Clinical Evidence". Menopausal Symptoms. *Br Med J* 2000; 321: 1516-1519.
- 6) GODSLAND IF. Effects of postmenopausal hormone replacement therapy on lipid, lipoprotein, and apolipoprotein (a) concentrations: analysis of studies published from 1974-2000. *Fertil Steril* 2001; 75: 898-915.
- 7) THE WRITING GROUP FOR THE PEPI TRIAL. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* 1995; 273: 199-208.
- 8) WALSH BW, SCHIFF I, ROSNER B, GREENBERG L, RAUNIKAR V, SACKS FM. Effects of postmenopausal estrogen replacement on the concentration and metabolism of lipoproteins. *New Engl J Med* 1991; 325: 1196-1204.
- 9) TIBOLONE (LIVIAL). A new steroid for the menopause. *Drug Ther Bull* 1991; 29: 77-78.
- 10) ALBERTAZZI P, DI MICCO R, ZANARDI E. Tibolone: a review. *Maturitas* 1998; 30: 295-305.
- 11) MODELSKA K, CUMMINGS S. Tibolone for postmenopausal women: systematic review of randomised trials. *J Clin Endocrinol Metab* 2002; 87: 16-23.
- 12) KICOVIC P, CORTÉS-PRIETO M, MILOJEVIC S, FRANCHI F. Placebo-controlled cross-over trial study of effects of Org OD 14 in menopausal women. *Reproduction* 1982; 6: 81-91.
- 13) NEVINNY-STICKEL J. Double-blind cross-over study with Org OD 14 and placebo in postmenopausal patients. *Arch Gynecol* 1983; 234: 27-31.
- 14) BEDENEK-JASZMANN LJ. Long-term placebo-controlled efficacy and safety study of Org OD 14 in climacteric women. *Maturitas* 1987; Suppl 1: 25-33.
- 15) LAAN E, VAN LUNSEN RH, EVERAERD W. The effects of tibolone on vaginal blood flow, sexual desire and arousability in postmenopausal women. *Climacteric* 2001; 4: 28-41.
- 16) GEUSENS P, DEQUEKER J, SCHOT LP. Non-linear increase in vertebral density induced by a synthetic steroid (Org OD 14) in women with established osteoporosis. *Maturitas* 1991; 13: 155-162.
- 17) BJARNASON N, BJARNASON C, CHRISTIANSEN C. The response in spinal bone mass to tibolone treatment is related to bone turnover in elderly women. *Bone* 1997; 20: 151-155.
- 18) BERNING B, KUIJK JW, BENNINK HJ, KIKOVIC PM, FAUSER BC. Effects of two doses of tibolone on trabecular and cortical bone loss in early postmenopausal women: a two-year randomized, placebo-controlled study. *Bone* 1996; 19: 395-399.
- 19) GALLAGHER J, BAYLINK DJ, NCCLUNG M. Prevention of bone loss with tibolone in postmenopausal women: results of two randomized, double-blind, placebo controlled, dose-finding studies. *J Clin Endocrinol Metab* 2001; 86: 4717-4726.
- 20) WALKER I, DAVIDSON A, YATES R, McEWAN HP. The effect of the synthetic steroid Org OD 14 on fibrinolysis and blood lipids in postmenopausal women. *Thromb Haemost* 1985; 53: 303-305.
- 21) GENAZZANI AR, PETRAGLIA F, GENAZZANI AD, BERGAMASCHI M, GRASSO A, VOLPE A. Effects of Org OD 14 on pituitary and peripheral β -endorphin in castrated rats and post-menopausal women. *Maturitas* 1987; Suppl 1: 35-48.
- 22) BJARNASON N, BJARNASON KH, BENNINK HJ, CHRISTIANSEN C. Tibolone: influence on markers of cardiovascular disease. *J Clin Endocrinol Metab* 1997; 82: 1752-1756.
- 23) LLOYD G, MCGING A, PATEL N, LUMB PJ, WIERZBICKI AS, JACKSON G. A randomised placebo controlled trial of the effects of tibolone on blood pressure and lipids in hypertensive women. *J Hum Hypertens* 2000; 14: 99-104.
- 24) VON ECKARDSTEIN A, CROOK D, ELBERS J, et al. Tibolone lowers high density lipoprotein cholesterol by increasing hepatic lipase activity but dose not impair cholesterol efflux. *Clin Endocrinol* 2003; 58: 49-58.
- 25) CETINKAYA MB, ALPER T, KOKCU A, YANIK FF, MALATYALIOGLU E. Tibolone versus four estrogen replacement therapy protocols and plasma lipid levels in postmenopausal women. *Int J Gynaecol Obstet* 2002; 79: 17-23.

- 26) DÖREN M, RÜBIG HJ, HOLZGREVE W. Resistance of pelvic arteries and plasma lipids in postmenopausal women: comparative study of tibolone and continuous combined estradiol and norethindone acetate replacement therapy. *Am J Obstet Gynecol* 2000; 183: 575-582.
- 27) BERNING B, KUIJK HJ, FAUSER BC. Absent correlation between vaginal bleeding and oestradiol levels or endometrial morphology during tibolone use in early postmenopausal women. *Maturitas* 2000; 35: 81-88.
- 28) HAMMAR M, CHRISTAU J, RUD T, GARRE K. A double-blind, randomised trial comparing the effects of tibolone and continuous combined hormone replacement therapy in postmenopausal women with menopausal symptoms. *Br J Obstet Gynaecol* 1998; 105: 904-911.
- 29) WINKLER U, ALTKEMPER B, HELMOND FA, COELINGH BENNINK HJ. Effects of tibolone and continuous combined hormone replacement therapy on parameters in the clotting cascade: a multicenter, double-blind, randomised study. *Fertil Steril* 2000; 74: 10-19.
- 30) MCCOY N, DAVIDSON JM. A longitudinal study of the effects of menopause on sexuality. *Maturitas* 1985; 7: 203-210.
- 31) CRONA NGL, SAMSIOE UB, SILFVERSTOLPE G. Treatment of climacteric complaints with Org OD 14: a comparative study with oestradiol valerate and placebo. *Maturitas* 1988; 9: 303-308.
- 32) TIMMER CJ, HOUWING NS. Dose proportionality of three different doses of tibolone. *Pharmacotherapy* 2002; 22: 6-13.
- 33) WU MH, PAN HA, WANG ST, HSU CC, CHANG FM, HUANG KE. Quality of life and sexuality changes in postmenopausal women receiving tibolone therapy. *Climacteric* 2001; 4: 314-319.
- 34) KANNEL WB, WILSON PW. Efficacy of lipid profiles in prediction of coronary disease. *Am Heart J* 1992; 124: 768-774.
- 35) WIEGRATZ I, STARFLINGER F, TETZLOFF W, et al. Effect of tibolone compared with sequential hormone replacement therapy on carbohydrate metabolism in postmenopausal women. *Maturitas* 2002; 41: 133-141.
- 36) CAGNACCI A, MALLUS E, TUVERI F, CIRILLO R, SETTENERI AM, MELIS GB. Effect of tibolone on glucose and lipid metabolism in postmenopausal women. *J Clin Endocrinol Metab* 1997; 82: 251-253.

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