Tibolone reverses the cognitive effects caused by leuprolide acetate administration, improving mood and quality of life in patients with symptomatic uterine leiomyomas

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Objective: To investigate the effects of tibolone co-administration with GnRH agonist treatment in terms of cognition, mood, and quality of life.
Design: Randomized, controlled, single-blind, clinical trial.
Setting: Department of gynecology and obstetrics at a university in Italy.
Patient(s): One hundred ten premenopausal women with symptomatic uterine leiomyomas.
Intervention(s): Six months of treatment with leuprolide acetate depot (11.25 mg IM, every 3 mo) associated with either tibolone (2.5 mg/d orally; group A) or placebo (1 tablet per d; group B).
Main Outcome Measure(s): At baseline and after 6 months of treatment, uterine and leiomyoma sizes, leiomyoma-related symptoms, climacteric-like symptoms, cognition, mood, and quality of life.
Result(s): At study entry, no difference was detected between groups in any parameters assessed. After treatment, the leiomyoma-related symptoms were significantly reduced in both groups, without any statistically significant differences between them. The Kupperman Index was statistically significantly higher in group B in comparison with baseline and group A. The cognition scores were statistically significantly different in comparison with baseline in group B, whereas no change was observed in group A. After treatment, mood and quality of life were statistically significantly improved in both groups, even though the improvement was significantly higher in group A than in group B.
Conclusion(s): Tibolone administration reverses the deleterious effect on cognition that is caused by leuprolide acetate depot and improves mood and quality of life in patients who receive GnRH agonist for symptomatic uterine leiomyomas. (Fertil Steril® 2008;90:165–73. ©2008 by American Society for Reproductive Medicine.)

Key Words: Cognition, GnRH-a, leuprolide acetate, mood, SNC, tibolone

The hypoestrogenic state induced by the use of GnRH analogue (GnRH-a) administration is effective in the treatment of several sex hormone–related diseases, such as precocious puberty (1, 2), breast cancer (3), symptomatic endometriosis (4), uterine leiomyomas (5), and severe premenstrual syndrome (6).

Moreover, GnRH-a treatments are related to several side effects consisting of climacteric-like symptoms, metabolic alterations, and, above all, bone loss (7). Even if poorly studied, other GnRH-a–related side effects consisting of impairments of neuropsychological functions also have been demonstrated (8–15). In fact, a close relationship has been shown between GnRH-a use and both reduction of cognitive functions (8–11, 14, 15) and occurrence of mood disorders (13, 14). A recent study (14) showed that the use of leuprolide acetate depot (LAD), a GnRH-a that is widely used in clinical practice, induces deleterious effects on cognition and mood in premenopausal women with symptomatic uterine leiomyomas, despite a significant improvement in quality of life that probably is a result of its therapeutic efficacy.

The association of low doses of sex hormones with GnRH-a (*add-back therapy*) may reduce the incidence and the severity of several analogue-related side effects (7), although only estrogens have been demonstrated to be effective in improving the neuropsychiatric functions in patients who receive GnRH-a (9, 11, 14, 15).

Tibolone, a synthetic compound that is structurally related to norethynodrel and that has weak estrogenic, androgenic, and progestinic properties, has been successfully associated with LAD for long-term treatment of premenopausal women with symptomatic uterine fibroids, resulting in a therapeutic efficacy similar to that of GnRH-a alone, reducing vasomotor symptoms and preventing bone loss, without any specific change in the lipid profile alone (16–19).

Our long-term clinical experience regarding the treatment of symptomatic patients with uterine leiomyomas by using

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GnRH-a plus tibolone association suggests a beneficial effect of tibolone on mental well-being and on quality of life. This hypothesis is supported by scientific data that highlight a beneficial effect of tibolone on memory, mood, and quality of life in postmenopausal women (20–24).

On the basis of these considerations, the present study was designed to investigate whether tibolone administration exerts beneficial effects on cognitive functions, mood, and quality of life in patients who receive GnRH-a for the treatment of symptomatic uterine leiomyomas.

MATERIALS AND METHODS

Subjects

Between January 2005 and February 2006, 145 premenopausal women affected by symptomatic uterine leiomyomas were screened for enrollment in the current study. Symptomatic uterine leiomyomas were clinically diagnosed and confirmed by ultrasonography.

The exclusion criteria were as follows: presence of neoplastic, metabolic (including glucose intolerance and dyslipidemia), infectious, or blood coagulation diseases and/or psychiatric disorder as determined by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (25, 26); a history of acute or recurrent vascular thrombosis; a body mass index (kg/m^2) of <18 or >30; a bone mineral density value of <1.0 of the SD of the mean bone density of the peak value for gender-matched healthy young adults (-1.0 T-score) at the posterior-anterior lumbar spine; a current or past history of acute or chronic physical illness; a premenstrual syndrome; and a present or past (<6 mo from study enrollment) use of hormonal drugs or drugs influencing cognition, vigilance, and/or mood.

Randomization

At study entry, all eligible subjects were enrolled into a randomized, single-blind, placebo-controlled study design.

The randomization was performed by using computer software (University of Catanzaro) that generated a random allocation sequence (a single sequence of random assignment). The random allocation sequence was created by using the single blocks as a method of restriction and then was concealed in opaque envelopes until the interventions were assigned.

The single-blinding was maintained throughout all of the study period.

Treatments

The subjects were assigned to one of two treatment groups. All women received LAD (Enantone; Takeda, Rome, Italy) at a dose of 11.25 mg IM every 3 months. At the same time, either tibolone (Livial, 2.5 mg/d orally; Organon, Rome, Italy; group A) or placebo tablets (1 tablet per d; group B) were administered.

The duration of the study was 6 months.

Protocol

At baseline and after 6 months of treatment, in each patient, anthropometric measurements; uterine dimensions; and number, dimensions, and location of uterine leiomyomas were assessed, and alcohol consumption, cigarettes smoked, years of education, work and socioeconomic status, and leiomyoma-related and climacteric-like symptoms were evaluated by the same clinician (A.F.) (27). During the same visits, another investigator (R.O.), who was aware of group assignment, gave the neuropsychological tests and asked each patient to report the onset of any adverse experience or any other specific experiences in a daily diary.

All women agreed to use barrier contraception throughout the study.

Ethics

The procedures used in the present study protocol were in accordance with the guidelines of the Helsinki Declaration on human experimentation. No study approval was required because we routinely use GnRH-a administration in clinical practice to treat patients with symptomatic uterine fibroids who want to avoid surgery, and all available data on the tibolone addition show its benefits in terms of reduction of GnRH-a–related side effects.

Before beginning the study, the purpose of the protocol was explained to all patients, and their written consent was obtained. The written informed consent included a careful and impartial description of the benefit–risk ratio for the analogue treatment and for the tibolone co-administration.

Ultrasonographic Evaluations

Ultrasonographic evaluations were performed by the same operator with an ultrasonographic scanner (Aplio; Toshiba Medical Systems, Rome, Italy) that was equipped with a 7.5-MHz vaginal probe.

Uterine and leiomyoma dimensions were calculated by measuring the main diameters (D_1, D_2, and D_3) and applying the formula of the ellipsoid ($D_1 \bullet D_2 \bullet D_3 \bullet 0.52$). An arithmetic mean of the sizes was used in presence of more than one leiomyoma. The changes in uterine and leiomyomas sizes were expressed as percent change from baseline values.

Leiomyoma-Related and Climacteric-Like Symptoms

Each woman was instructed to record in a personal daily diary the severity of the leiomyoma-related symptoms by using a rank scale, ranging from 1 to 10 (16, 17).

The climacteric-like symptoms were evaluated by using the Kupperman Index (KI) (28). The KI (score range, 0–51) assesses 11 symptoms: vasomotor symptoms, paresthesia, insomnia, nervousness, melancholia, vertigo, weakness, arthralgia and myalgia, headache, palpitations, and fornication.