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Prevention of bone loss and hypoestrogenic symptoms by estrogen and interrupted progestogen add-back in long-term GnRH-agonist down-regulated patients with endometriosis and premenstrual syndrome

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ABSTRACT

Objective: To examine the utility of a low-dose estrogen and pulsed progestogen hormone replacement therapy (HRT) regimen for add-back during long-term gonadotropin-releasing hormone-agonist (GnRH-agonist) therapy.

Design: A pilot clinical trial conducted at a tertiary referral, academic, reproductive sciences center. The study included 15 patients with endometriosis and 5 patients with severe premenstrual syndrome (PMS). Patients with endometriosis received leuprolide acetate depot 3.75 mg IM monthly until their symptoms had resolved (2–3 months), at which time HRT was initiated along with the GnRH-agonist. Patients with severe PMS received the same treatment with the addition of HRT after 1 month. The HRT regimen consisted of 1 mg oral micronized estradiol daily and 0.35 mg norethindrone daily for 2 days alternating with 2 days without norethindrone. The main outcome measure included bone density assessment in the lumbar spine and femoral neck by dual-energy x-ray absorptiometry at 6- to 12-month intervals. The mean follow-up duration ± SD while on GnRH-agonist treatment was 31.2 ± 17 months (for endometriosis patients) and 37.7 ± 8.4 months (for patients with severe PMS).

Results: Bone mineral density was stable after initiation of HRT for the entire follow-up period. No patient had return of pelvic pain or resumption of mood swings after HRT add-back. After the first 3 months of HRT, all women remained amenorrheic.

Conclusions: Long-term GnRH-agonist down-regulation is safe and effective when combined with HRT add-back. Furthermore, on the basis of this small study, the low-dose pulsed progestogen, continuous estrogen HRT regimen seems to be safe for use as add-back therapy in terms of bone health.

Key Words: HRT addback – Endometriosis – GnRH-agonist – HRT – Premenstrual syndrome.

Gonadotropin-releasing hormone agonists (GnRH-agonists) have proved to be extremely efficacious in treating gonadal steroid-dependent problems, such as endometriosis, uterine leiomyoma, premenstrual syndrome (PMS), precocious puberty, and prostate and breast cancers. Their short-term use (<6 months) has resulted in very few side effects. Long-term use may, however, lead to skeletal calcium loss and decreased bone mineral density (BMD) as a consequence of hypoestrogenism.[1] Endometriosis, the second most common gynecologic disorder after leiomyomas, is found in 2% to 5% of the general population.[2,3] The pathogenesis and treatment options (medical vs. surgical) of endometriosis have been controversial. However, GnRH-agonists have proven highly efficacious for management of pain associated with endometriosis,[4–8] with

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similar or superior results compared with other available forms of medical management.[9,10] PMS is another frequent gynecologic disorder, the exact pathophysiology of which remains to be determined. It is generally accepted that cyclic changes in the blood levels of sex hormones play a pivotal role,[11] and most patients affected by PMS report complete resolution of symptoms during therapy with GnRH-agonists.[12,13]

The success of GnRH-agonists in treating these conditions relies on inducing a state of hypogonadotropic hypogonadism by down-regulating the pituitary GnRH receptors. However, a major problem limiting the long-term use of these agents is the severe hypoestrogenism with associated irreversible loss of bone, which may occur with prolonged (>6 months) treatment.[14,15]

Hormone replacement therapy (HRT) add-back during treatment with GnRH-agonists may prevent bone loss and other symptoms of estrogen deficiency without reactivating the underlying pathologic process, if administered in an appropriate dosage and schedule. The rationale for this approach is the "estrogen threshold hypothesis" first suggested by Barbieri in 1990.[16] According to this hypothesis, adding back small amounts of estrogen will maintain bone density and relieve vasomotor symptoms, whereas estrogen-dependant pathologies, such as endometriotic lesions, will remain quiescent because estrogen levels are below the threshold needed to reactivate them.[16]

We previously reported the novel regimen of the combination of continuous estrogen with interrupted or pulsed progestogen for HRT.[24–30] The combination of continuous estrogen with interrupted progestogen seems to result in increased sensitivity to estrogen and progestogen in estrogen-responsive tissues. As a result, lower doses of estrogen and progestogen may be used for HRT with good biological effects. The objective of the present study was to examine the utility of the new low-dose estrogen and pulsed progestogen HRT regimen for add-back in a group of young women on prolonged GnRH-agonist therapy and to test the hypothesis that HRT add-back prevents hypoestrogenic adverse effects but does not reduce the clinical efficiency of long-term GnRH-agonists for severe PMS or endometriosis.

METHODS

Approval was obtained from the Research Ethics Board of the University of Toronto for the use of the HRT regimen described below. Patients were enrolled in the study at the Reproductive Biology Unit, Division of Reproductive Sciences, Department of Obstetrics and Gynecology, University of Toronto, Canada.

This study was an observational clinical trial that included 15 patients with endometriosis and 5 patients with severe PMS. None of the women wished to conceive, but all of them were anxious to preserve their fertility at the time of their initial consultation. Endometriosis patients sought medical treatment because of pelvic pain, dyspareunia, and dysmenorrhea associated with endometriosis, which was confirmed by laparoscopy and histopathology. Ten of the 15 patients with endometriosis had undergone multiple laparoscopic surgeries or laparotomies for management of endometriosis before medical management. Women with severe PMS were enrolled in the study after exclusion of psychiatric disorders or other health problems by history and physical and pelvic examination. PMS severity was defined according to symptom charting for at least two cycles using the Prospective Record of the Impact and Severity of Menstrual Symptomology calendar and a six-item linear analog scoring system for the documentation of PMS, as previously described.[31] For the diagnosis of severe PMS, the women had to have symptoms of such a degree that employment or social interactions were compromised. None of the patients had used any hormonal therapy, including GnRH-agonists, during the 3 months before starting the study. However, all the patients had tried at least one of the commonly applied therapies for PMS, such as oral contraceptive pills or, more recently, serotonin reuptake inhibitors. Alternative therapies were discussed with the patients before starting the use of GnRH-agonist treatment. All subjects were nonsmokers. The mean age ± SD of the patients at the beginning of the GnRH-agonist treatment was 31.9 ± 6.1 years (for endometriosis patients) and 34.7 ± 7.5 years (for patients with severe PMS). The age ranged from 18.3 to 40.5 years (for endometriosis patients) and from 26.4 to 46.8 years (for patients with severe PMS). The mean follow-up duration ± SD for the patients while on GnRH-agonist treatment was 31.2 ± 17 months (for endometriosis patients) and 37.7 ± 8.4 months (for patients with severe PMS). The follow-up duration ranged from 26.4 months to 46.8 months (for endometriosis patients) and from 14.4 months to 58.8 months (for patients with severe PMS).

After exclusion of pregnancy by determination of a negative serum β-human chorionic gonadotropin, GnRH-agonist treatment was started. Women with endometriosis received leuprolide acetate depot 3.75 mg (Lupron, TAP Pharmaceuticals, Lake Forest, Ill., USA) IM monthly until their pelvic pain and dyspareunia had resolved to the point that the women considered themselves subjectively symptom-free (2–3 months), at

which time HRT add-back was started along with the GnRH-agonist. For the patients with severe PMS, the same treatment was used with the addition of HRT add-back after 1 month of GnRH-agonist injection. In all patients, GnRH-agonist injections were started during the luteal phase of the menstrual cycle. The HRT regimen consisted of oral administration of 1 mg micronized estradiol (E_2) (Estrace, Roberts Pharmaceutical, Mississauga, Ontario, Canada) daily and 0.35 mg norethindrone (Micronor, Ortho/MacNeil, Raritan, NJ, USA) daily for 2 days alternating with 2 days without progestogen. The women were counseled to maintain adequate calcium intake by diet. Calcium supplements of 500 mg to 1,000 mg daily were prescribed if calcium intake seemed low by diet alone.

The primary outcome measure of this study was a change in BMD, calculated from measured bone mineral content, because a significant decline in BMD would necessitate a discontinuation of GnRH-agonist treatment. Bone density in the lumbar spine (L1–L4) and in the femoral neck was assessed by dual-energy x-ray absorptiometry (DEXA) (Hologic 1000, Hologic Corporation, Waltham, Mass., USA) at 6- to 12-month intervals for up to 5 years in some women. During this time, the same two technicians performed all DEXA scans. The Hologic equipment was calibrated daily using a standard bone "phantom." The coefficient of variation for the BMD calculation was 1%. Secondary outcome measures were symptom control and bleeding patterns, which were recorded on diary cards and assessed during regular follow-up clinic visits every week during the first month of treatment, then monthly for the first 6 months and every 3 to 6 months thereafter.

Statistics

The BMD results were compared between the start and end of GnRH-agonist treatment by paired two-tailed student's *t* test. The statistical tests were performed with GraphPad Prism Version 3 software (GraphPad Software Inc., San Diego, Calif., USA).

RESULTS

All patients had subjective resolution of their endometriosis-associated pain within 2 to 3 months of starting the GnRH-agonist injections. The five women with severe PMS had no further evidence of luteal dysphoria as determined by Prospective Record of the Impact and Severity of Menstrual Symptomology calendar or visual analogue scales after the first month on GnRH-agonist treatment. No patient had return of pelvic pain or resumption of mood swings after HRT add-back. After the first 3 months, all women in this study remained amenorrheic with the exception of occasional spotting.

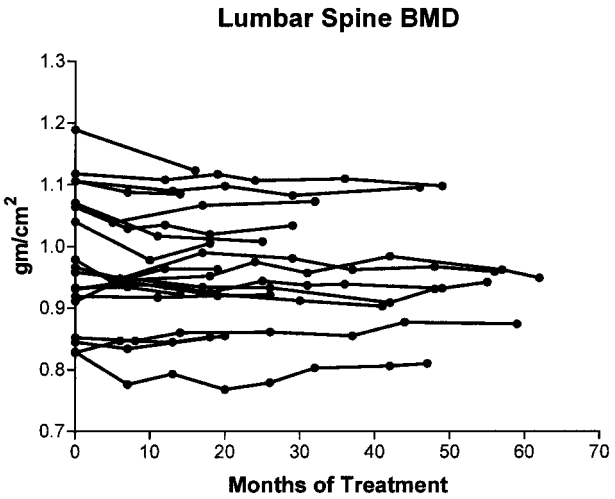

FIG. 1. Bone mineral density (BMD) in the lumbar spine measured by dual-energy x-ray absorptiometry (DEXA) serially in individual patients with endometriosis and premenstrual syndrome (PMS).

The BMD in the lumbar spine (Fig. 1) and in the femoral neck (Fig. 2) remained relatively stable throughout the follow-up period for each patient enrolled in the study. None of the patients lost a clinically significant percentage of BMD during the study (i.e., >3%). For the group as a whole, there was no significant difference between the mean (±SD) bone density in the lumbar spine or in the femoral neck at end of treatment compared with the beginning (baseline BMD) of GnRH-agonist treatment (Fig. 3).

None of the patients dropped out of the study or reported any serious side effects or complaints regarding the treatment. All women with less than 2 years of follow-up discontinued treatment to conceive, and those who stopped after more than 2 years generally did so to undergo definitive surgical therapy (hysterectomy and bilateral salpingo-oophorectomy).

DISCUSSION

Despite the high success rate of GnRH-agonist treatment in alleviating endometriosis symptoms, discontinuation of GnRH-agonist treatment is associated with up to a 75% recurrence of symptoms in women with severe disease,[32] usually within 6 months after stopping GnRH-agonist treatment.[33] This leads to the potential need to continue GnRH-agonist administration for long periods in many patients for them to remain pain free. Other conditions, such as PMS and fibroids, also require long-term treatment. However, GnRH-

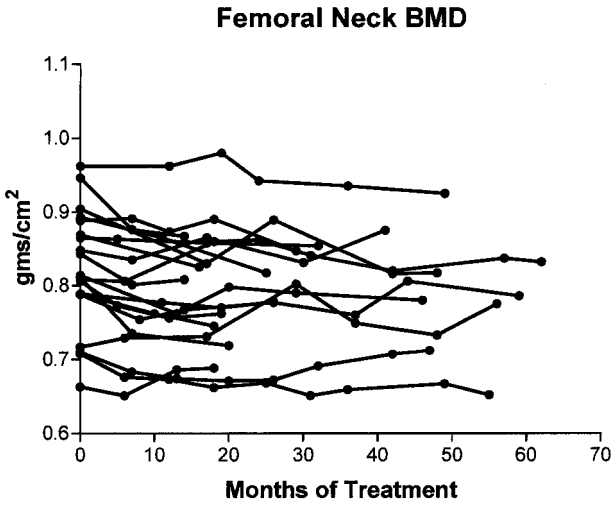

FIG. 2. Bone mineral density (BMD) in the femoral neck measured by dual-energy x-ray absorptiometry (DEXA) serially in individual patients with endometriosis and premenstrual syndrome (PMS).

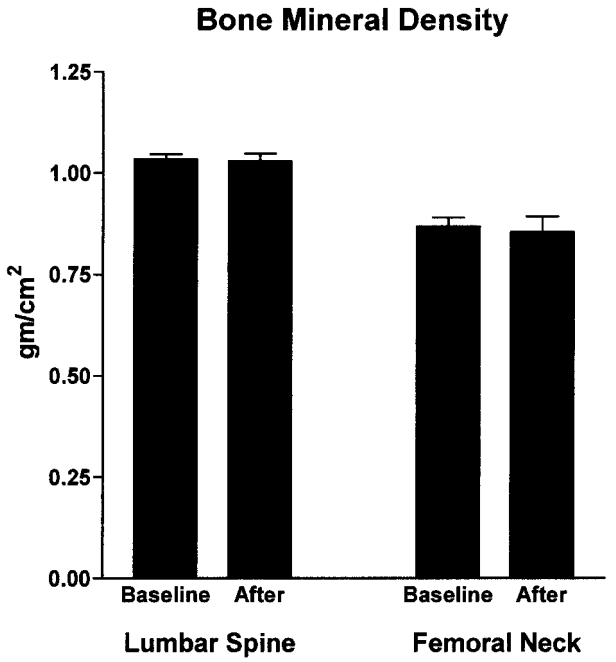

FIG. 3. Mean (±SD) bone mineral density (BMD) measured by dual-energy x-ray absorptiometry (DEXA) in lumbar spine and femoral neck before initiation of GnRH-agonist treatment (baseline) and at last study visit (after).

agonist treatment is not recommended for periods longer than 6 months because of the development of complications, the most important of which is loss of BMD that may be irreversible after 6 months of GnRH-agonist treatment.[14,15] Moreover, the hot flushes, vaginal dryness, and other symptoms related to hypoestrogenism associated with GnRH-agonist treatment are distressing and lead to discontinuation of treatment in a considerable proportion of cases. Psychiatric problems, including depression, anxiety, and mood disorders, were also found to be associated with long-term treatment with GnRH-agonist.[34–36] HRT add-back has been hypothesized to minimize or eliminate hypoestrogenic side effects while preserving the therapeutic efficacy of GnRH-agonist treatment.[16,37]

The HRT add-back hypothesis is based on the results of several studies, which have investigated a combination of estrogen and progestogen supplementation (and other regimens, such as progestogen only) in patients treated with GnRH-agonist for various gynecologic conditions. HRT add-back treatment was reported to be successful in preventing the hypoestrogenic symptoms without affecting the clinical improvement of endometriosis and uterine leiomyomas.[17–21] However, there is still some debate regarding the use of HRT add-back with GnRH-agonist treatment for severe PMS. One study showed that the combination of E_2 valerate and norethisterone given continuously as add-back therapy resulted in a worsening in the clinical response in patients with severe PMS treated with GnRH-agonists.[22] The regimen of the present study contained norethisterone 0.35 mg in an interrupted or pulsed regimen together with 1 mg of micronized E_2 daily. This regimen resulted in a total progestogen dose almost threefold lower than the lowest dose of norethisterone-containing HRT preparation currently available. The reduced progestogen dose may explain in part the observed beneficial effect on PMS symptoms. A more recent randomized study reported the success of tibolone administered in association with GnRH-agonist in preventing the hypoestrogenic symptoms without reducing the therapeutic effect of GnRH-agonist in women affected by PMS.[23] Despite the small number of patients included in our series, those with severe PMS were followed up for a long duration (15–40 months) and the results suggest clinical efficacy of combining GnRH-agonist treatment with HRT add-back therapy for long-term treatment. Similar results pertain to the women with endometriosis who have been followed up for periods of up to 5 years without loss of BMD and no return of endometriosis-related symptoms.

Surrey recently suggested that there is no benefit in deferring initiation of add-back treatment until the agonist takes effect or until the patient complains of side effects.[37] This opinion is based on the results of different randomized trials that demonstrated similar efficacy in patients who received either GnRH-agonist alone or with concomitant initiation of add-back.[38–41]

We agree with this approach, which is now our current treatment regimen. At the time of enrollment of women into the present study, however, our practice was to wait for resolution of endometriotic or PMS symptoms before starting add-back HRT therapy.

In this study, we chose to examine continuous estrogen with interrupted progestogen for HRT add-back based on the principle of increasing estrogen and progestogen efficacy at low doses by using estrogen and progesterone receptor fluctuations. The interrupted or pulsed progestogen regimen does seem to result in the postulated maintenance of steroid receptors and continuing sensitivity of estrogen-responsive tissues with supportive data obtained in animal studies and in preliminary clinical trials.[24] We hypothesized that the new regimen would also be beneficial in terms of bone effects because progestogen has a synergistic effect with estrogen on BMD, resulting in greater bone density than estrogen alone.[28] Androgen also increases bone density in a primate model of polycystic ovarian syndrome.[42] In orchidectomized rats, the nonaromatizable androgen dihydrotestosterone increases bone density[43] and also stimulates proliferation of osteoblasts in vitro.[44] Norethindrone in large doses has some androgenic activity. However, we believe the dose used in the present study is far below that giving an androgenic effect clinically, as demonstrated by the lack of negative effect on high-density lipoprotein cholesterol seen with the same dose of norethindrone used in another clinical trial.[30] In addition, using an aged rat model of osteopenia, we demonstrated that bone density could be maintained equally well with norgestimate, a nonandrogenic progestogen,[26] and with low doses of norethindrone, having no androgenic effect in a sensitive in vivo rat prostate and seminal vesicle weight assay.[28]

In our present study, a low-dose HRT add-back regimen in which progestogen was administered on a pulsed or interrupted basis together with continuous estrogen seemed to give good long-term results from the aspects of both efficacy and safety. Some of the patients were followed up for treatment periods of up to 6 years with maintained clinical improvement of endometriosis and PMS-associated symptoms and with preservation of bone density. Our study was an observational clinical trial, in which the study patients were not randomized against a placebo group, an obvious weakness in terms of conclusions regarding effectiveness. Therefore, larger controlled studies are needed to determine the safety and effectiveness of very long-term GnRH-agonist and HRT add-back treatment and can likely only be accomplished through multicenter collaboration.

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