Introduction

Endometriosis, a common gynecological condition causing cyclical pain, dyspareunia, and infertility, affects 2% to 5% of women of reproductive age. Endometriosis commonly recurs after medical or surgical treatment; in the absence of a drug treatment that is safe for long-term use, recurrence can lead to hysterectomy and bilateral oophorectomy. Goals of therapy include relief of symptoms, resolution of existing lesions, and prevention of new lesions. Gonadotropin-releasing hormone agonist (GnRH-a) is increasingly used to treat endometriosis.

Therapy with GnRH-a achieves hypoestrogenism and amenorrhea by suppressing pituitary gonadotropin secretion, Several studies have shown that use of GnRH-a promotes subjective and objective improvements in endometriosis related symptoms.

Prolonged treatment is often required to achieve clinically significant effects on endometriosis symptoms. However, there is concern about the clinical, physical, and biochemical side effects of hypoestrogenism, particularly the rapid reduction in bone mineral density (BMD) that could increase the risk of osteoporosis. Thus, the use of GnRH-a is generally restricted to a 6-month course.

GnRH-a related hypoestrogenism frequently causes climacteric-like symptoms, such as vasomotor symptoms and overall severe bone loss. Several drugs have been associated with GnRH-a to reduce these side effects and to

Raloxifene Administration in Women Treated with Long Term Gonadotropin-releasing Hormone Agonist for Severe Endometriosis: Effects on Bone Mineral Density

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Objectives: To evaluate the efficacy of raloxifene in preventing bone loss associated with long term gonadotropin-releasing hormone agonist (GnRH-a) administration.

Methods: Twenty-two premenopausal women with severe endometriosis were treated with leuprolide acetate depot at a dosage of 3.75 mg/4 weeks, for 48 weeks. Bone mineral density (BMD) was evaluated at admission, and after 12 treatment cycles.

Results: At cycle 12 of GnRH-a plus raloxifene treatment, lumbar spine, trochanter femoral neck, and Ward’s BMD differed from before the treatment. A year after treatment, the lumbar spine and trochanter decreased slightly, but were not significantly different.

Conclusions: Our study shows that the administration of GnRH-a plus raloxifene in pre-menopausal women with severe endometriosis, is an effective long-term treatment to prevent bone loss. (J Menopausal Med 2016;22:174-179)

Key Words: Bone mineral density · Endometriosis · Gonadotropin-releasing hormone agonist · Raloxifene hydrochloride
Raloxifene hydrochloride is a synthetic non-steroidal drug derived from benzothiophene and afferent to selective estrogen receptor modulators (SERMs), a group of compounds that interact with estrogen receptors eliciting tissue-specific responses.

Raloxifene acts on the metabolism, central nervous system, skeleton and cardiovascular system as an estrogenic agonist, whereas it shows a weak estrogenic antagonist effect on reproductive organs, including the breast and uterus. Therefore, raloxifene has been used as a therapeutic agent for osteoporosis.

Continuous administration of GnRH-a inhibits the release of gonadotropins inducing a down-regulation of pituitary GnRH receptors and a state of hypogonadotropic hypogonadism.

Thus far, there has been limited research regarding raloxifene administration for the prevention of the bone loss associated with GnRH-a. The aim of this study was to evaluate whether the bone loss that occurs when using GnRH-a could be prevented.

**Materials and Methods**

1. **Patient selection**

   The present study was conducted in the department of obstetrics and gynecology at Chosun University Hospital. From January 2012 to December 2015, 22 reproductive female patients from 25 to 51 years old who suffered from endometriosis were enrolled in a non-randomized retrospective study.

   Exclusion criteria were as follows: patients with BMD below the age-matched normal range (z-score below −1.5), who had physical findings that affected the measurement of BMD, such as fracture or osteoarthritis of spine, and who were administered drugs that affected bone turnover, or who received therapy for endometriosis within 4 weeks prior to the start of the study. Written consent from the patient was obtained before enrollment.

   Thirty-two patients were enrolled in this study. Four patients discontinued leuprolide administration due to adverse effects or undesirable complications. Two patients were excluded because hormone drugs (oral pill) had been administered within 4 months prior to the start of treatment, and four patients were excluded because BMD was not measured correctly. Thus, the analysis was performed on 22 patients.

2. **Treatment protocol**

   At the start of the study, all subjects were randomized in a study design using a computer–generated randomization list. The subjects were assigned to 22 women. All women received leuprolide acetate depot (LAD) (Enantone; Takeda, Rome, Italy) at a dose of 3.75 mg/4 weeks combined with raloxifene hydrochloride (Evista; Eli Lilly, Sesto Fiorentino, Italy) at a dose of 60 mg/day, p.o. The duration of the study was 12 cycles of 4 weeks each, and for this period, the single-blinding was maintained.

3. **Study protocol**

   BMD was measured at the beginning of the study and after cycle 12 treatment with GnRH-a plus raloxifene.

4. **BMD measurement**

   The BMD was determined using a prodigy series X-ray tube housing assembly (LUNAR, GE Medical system, Madison, WI, USA) at the posterior–anterior lumbar spine (vertebrae L1 to L4) and hip (trochanter, Ward’s and femoral neck).

   The results of absorptiometry were examined by a single observer blind to different treatment regimens. The primary end–point was the lumbar spine BMD, Hip trochanter, Ward’s and femoral neck BMD were considered secondary end–points.

5. **Statistical analysis**

   In this study, the paired t-test was used to compare the BMD differences of the lumbar spine, trochanter, femoral neck, and Ward’s in women before and 1 year after treatment with GnRH-a plus raloxifene. A P value of < 0.05 indicated statistical significance. Statistical analysis was performed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA).
Results

1. Demographic data
Twenty-two enrolled patients completed the study. All the patients had endometriosis diagnosed by laparoscopy. The classification of patients is shown in Table 1.

Subjects in this study had a mean body weight of 62.2 ± 10.2 kg, mean height of 159 ± 5.1 cm, and body mass index (BMI) of 24.7 ± 4.3 kg/m^2.

2. BMD measurements
We designed a prospective study and checked lumbar spine, trochanter, femoral neck, and Ward’s BMD in 22 patients at the start of the study and 1 year after treatment with GnRH-a plus raloxifene.

At cycle 12 of treatment with GnRH-a plus raloxifene, lumbar spine, trochanter, femoral neck, and Ward’s BMD differed from before treatment. The lumbar spine and trochanter decreased slightly at the 1 year after treatment than before (Table 2), but were not significantly different.

3. Side effects and drop-outs
Throughout the study, the treatment schedules were generally well tolerated. Raloxifene was well tolerated. No serious adverse experience was reported during the study. No drop-out was due to drug–related adverse experiences.

Discussion
Use of GnRH—a has an established place in the medical treatment of endometriosis. These agents act by down-regulating pituitary gonadotropins, resulting in the suppression of gonadotropin production and secondary ovarian suppression. This ovarian suppression may lead to osteopenia by reducing the BMD.

Accordingly, treatment with GnRH—a alone is generally restricted to 6 month duration because of concern about continuing loss of BMD over longer treatment periods. All studies agree that bone loss occurs with continued use of GnRH—a for 6 months or more.

Circulating estradiol levels decrease to the postmenopausal range, producing important menopausal side effects, such as a reduction in BMD at the lumbar spine and proximal femur. Therefore, there is a need for the prevention of bone loss during long term treatment with GnRH—a.

Raloxifene at the standard dosage of 60 mg daily prevents postmenopausal bone loss in women without osteoporosis and is used also to treat established postmenopausal osteoporosis.

Table 1. Demographic characteristics of subjects

| Characteristics       | Mean ± SD (n = 22) | Range (min-max) |
|-----------------------|--------------------|-----------------|
| Age (years)           | 40.4 ± 7.4         | 25-51           |
| Weight (kg)           | 62.2 ± 10.2        | 48-80           |
| Height (cm)           | 159 ± 5.1          | 148-166         |
| Body mass index (kg/m^2) | 24.7 ± 4.3       | 18.7-32.5       |
| Previous pregnancy    | 1.4 ± 0.8          | 0-3             |
| Treatment regimen     | LAD 3.75 mg/4 weeks + raloxifene 60 mg/day |

Table 2. Comparison of bone mineral density in women before, and 1 year after treatment with gonadotropin-releasing hormone agonist plus raloxifene

| BMD                  | Before (n = 22) | 1 year after (n = 22) | P value |
|----------------------|----------------|-----------------------|---------|
| T-score              |                |                       |         |
| Lumbar spine         | -0.732 ± 1.22  | -0.897 ± 1.22         | 0.065   |
| Trochanter           | 0.645 ± 1.67   | 0.335 ± 1.65          | 0.057   |
| Femoral neck         | 0.382 ± 1.47   | 0.432 ± 1.47          | 0.866   |
| Ward’s               | 0.24 ± 1.5     | -0.041 ± 1.63         | 0.099   |
| Z-score              |                |                       |         |
| Lumbar spine         | -0.991 ± 1.11  | -0.959 ± 1.4          | 0.072   |
| Trochanter           | 0.259 ± 1.45   | 0.068 ± 1.56          | 0.055   |
| Femoral neck         | 0.432 ± 1.47   | 0.509 ± 1.41          | 0.162   |
| Ward’s               | -1.068 ± 1.22  | 0.177 ± 1.65          | 0.108   |

The data is presented as mean ± standard deviation.
P < 0.05 versus baseline.
BMD: bone mineral density.
In addition, raloxifene reduces the risk of vertebral fractures in postmenopausal osteoporotic women with or without preexisting fractures by about 40% versus a placebo, thereby improving quality of life.

In women treated with GnRH–a, the positive effect of raloxifene on bone metabolism was also confirmed by the lack of significant change in biochemical parameters of bone formation and reabsorption. Goldstein et al. confirmed that raloxifene did not induce endometrial proliferation in postmenopausal women, unlike estrogen.

Besides, a variety of anti-reabsorptive drugs has been used to preserve the bone tissue during GnRH–a treatment. During our study period, few side effects were detected and raloxifene treatment was tolerated.

In the case of severe endometriosis, patients were administered GnRH–a for 6 months. However, sometimes the pain recurred after normal menstruation restarted. Therefore, a method of treating patients has not been fully established.

If necessary, the treatment could be administered in the oral pill, progestin but GnRH–a is known to suppress endometrial lesions and symptoms. Therefore, GnRH–a was administered with raloxifene to inhibit bone loss that was the greatest side effect of GnRH–a administration.

In a previous report, there was no change in BMD when a combination of GnRH–a and raloxifene was administered for six months, thereby the present study administered a combination of GnRH–a and raloxifene for 1 year in patients who suffered from pain.

BMD continues to decline rapidly during the early postmenopausal years.

The annual rates of loss during these intervals were approximately 1.8% to 2.3% in the spine and 1.0% to 1.4% in the hip.

Our findings suggest that BMD is reduced slightly over 1 year of treatment with GnRH–a and raloxifene, but was not statistically significantly different from the start of the study. Therefore, this treatment does not seem to affect bone loss significantly.

Some limitations of this study deserve mention. It has mostly stemming from a small number of sample, the absence of a control group, and retrospective design. Besides, fracture risk was not assessed.

In conclusion, our study shows that the administration of GnRH–a plus raloxifene in pre-menopausal women with severe endometriosis would be effective to prevent bone loss for long-term treatment. It is possible that raloxifene could be used as an ‘add-back therapy’ in women treated with GnRH–a.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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