International Journal of Gynecology & Obstetrics 54 (1996) 237–243

International Journal of GYNECOLOGY & OBSTETRICS

Article

Long-acting triptorelin for the treatment of endometriosis

W. Choktanasiri[a], W. Boonkasemsanti[b], T. Sittisomwong[b], S. Kunathikom[c], S. Suksompong[c], U. Udomsubpayakul[d], A. Rojanasakul*[a]

[a]*Department of Obstetrics and Gynecology, Ramathibodi Hospital, Bangkok, Thailand*
[b]*Department of Obstetrics and Gynecology, Chulalongkorn Hospital, Bangkok, Thailand*
[c]*Department of Obstetrics and Gynecology, Siriraj Hospital, Bangkok, Thailand*
[d]*Research Center, Ramathibodi Hospital, Bangkok, Thailand*

Received 27 December 1995; revised 3 April 1996; accepted 4 April 1996

Abstract

Objective: To evaluate the efficacy and adverse effects of monthly triptorelin injection for the treatment of endometriosis. *Methods:* A multicenter clinical trial including 45 women with endometriosis, treated with triptorelin 3.75 mg i.m. every 4 weeks in six consecutive doses. The main outcome measures were symptom relief, reduction according to revised American Fertility Society (rAFS) scores, reduction in size of ovarian endometrioma, effects on hormone and lipid profiles, changes in bone mineral density (BMD), adverse effects, and return of menstruation. Data were analyzed using repeated measures analysis of variance and paired *t*-tests. *Results:* Pain-related symptoms decreased in all cases after 8 weeks of treatment. Laparoscopic assessment revealed a reduction in rAFS scores in 21 out of 25 cases (mean pretreatment scores 43.44 ± 5.75 vs. post-treatment scores 22.30 ± 3.40, $P < 0.001$). The size of ovarian endometrioma decreased in eight of nine women but none disappeared. Serum luteinizing hormone, follicle-stimulating hormone and estradiol levels were effectively suppressed during treatment. A slight increase in cholesterol and triglyceride levels was observed but all values were within normal limits. After 24 weeks of treatment there was a slight decrease in BMD of total body, lumbar vertebrae and femoral neck but not radius. The main adverse effects included hot flushes, night sweating, vaginal dryness, headache, dizziness and nausea. Menstruation returned 83.76 ± 2.91 days after the last injection of triptorelin. *Conclusion:* Long-acting triptorelin is efficacious in the treatment of endometriosis and has tolerable side effects.

Keywords: GnRH agonist; Triptorelin; Decapeptyl CR; Endometriosis

1. Introduction

Endometriosis is a common gynecologic disorder affecting women in their reproductive years. Although at present no definite etiologic cause has been elucidated, it is beyond doubt that the ectopic endometrial growth is dependent on estrogen. Gonadotropin-releasing hormone agonists (GnRHa) effectively induce a reversible hypoestrogenic state which results in atrophic changes to ectopic endometrial tissue [1]. With GnRHa therapy, endometriosis is suppressed and the patient's symptoms are alleviated. GnRHa is

* Corresponding author, Tel: +66 2 2455828; Fax: +66 2 2011416.

0020-7292/96/$15.00
PII S0020-7292(96)02698-7

presently one of the established medical treatments for endometriosis [1–5].

Triptorelin is a potent GnRHa. Glycine at position 6 of the native hypothalamic GnRH is replaced by D-tryptophan. This structural change makes triptorelin 70–100 times more potent than the native GnRH [1]. Long-acting triptorelin is available for monthly injection. Since the hormonal treatment of endometriosis usually lasts for 6–9 months, a long-acting GnRHa preparation can be more convenient for the patient and therefore increase her compliance and acceptance. The aim of this study was to determine the efficacy and adverse effects of monthly triptorelin injections for the treatment of endometriosis.

2. Materials and methods

2.1. Study design

This was a multicenter clinical trial. The three reproductive endocrine units of Chulalongkorn, Siriraj and Ramathibodi University Hospitals were involved in the study.

2.2. Subjects

Forty-five women who suffered from mild to severe endometriosis were recruited to the study (15 patients per center). The diagnosis of endometriosis was made by either laparoscopy or laparotomy. No patient had any other medical disorder or had been treated by any hormone prior to the study. The severity of disease was classified using the revised American Fertility Society (rAFS) classification [6].

2.3. Treatment

All patients were treated with intramuscular injection of triptorelin (Decapeptyl CR; Ferring, Malmö, Sweden) 3.75 mg every 4 weeks in six consecutive doses. Treatment began during the first week of the menstrual cycle.

2.4. Assessments

Patients' assessments included symptom relief, reduction in rAFS scores, change in size of ovarian endometrioma, effects of triptorelin on hormone levels (luteinizing hormone [LH], follicle-stimulating hormone [FSH], estradiol), lipid profiles (cholesterol, triglyceride and high-density lipoprotein [HDL] cholesterol), bone mineral density (BMD), adverse effects of triptorelin and return of menses after discontinuation of GnRHa.

Pain symptoms (dysmenorrhea, dyspareunia and pelvic pain) were classified as mild, moderate or severe (Table 1).

Hormonal assays were determined before treatment and after 8 and 24 weeks of treatment by radioimmunoassay using commercial kits. The measurement of BMD was performed by dual energy X-ray absorptiometry (DEXA) before and immediately after treatment.

2.5. Data analysis

A preliminary descriptive data analysis was done to summarize the characteristics of the study subjects, followed by repeated measures analysis of variance and a post hoc Newman-Keuls test for hormone changes on GnRHa treatment. Paired *t*-tests were used to compare pre- and post-treatment values. Analyses were performed by computer using the statistical packages SPSS version 6.0.

Table 1
Classification of pain symptoms

Dysmenorrhea	
Mild	Partial inability to work
Moderate	Occasional bed rest and inability to work
Severe	At least one day of complete bed rest, inability to work
Dyspareunia	
Mild	Uneasiness, but tolerable
Moderate	Copulation so painful that has to be discontinued
Severe	Avoidance of copulation due to pain
Pelvic pain	
Mild	Occasional ache/pain in the pelvis
Moderate	Ache/pain during most of the menstrual cycle
Severe	Requirement of strong analgesics; pain persisting throughout the menstrual cycle, even when not menstruating

3. Results

Two patients were excluded from the study due to incomplete follow-up. The data from 43 patients were analyzed. The patients' characteristics are described in Table 2. All patients were of reproductive age. All but three patients had a body mass index (BMI) <25 kg/m^2. Among 43 patients, 22, 17 and four had severe, moderate and mild endometriosis, respectively. After 8 weeks of treatment, approximately 75% of patients became amenorrheic. All ceased menstruating after 10 weeks of treatment. In the majority of patients painful symptoms (dysmenorrhea, dyspareunia and pelvic pain) improved after the first month of treatment. Almost all patients were pain-free after 8 weeks of treatment (Fig. 1).

Triptorelin therapy reduced the pathology of disease in most cases. Reduction of endometriotic implants rather than adhesions was commonly observed. The rAFS scores were reduced in 21 out of 25 cases in whom second-look laparoscopy was performed. The mean pretreatment rAFS scores compared with post-treatment scores were 43.44 ± 5.75 vs. 22.30 ± 3.40 ($P < 0.001$) (Fig. 2).

The sizes of ovarian endometriomas measured by ultrasound were decreased in eight out of nine patients (Fig. 3). The mean diameter of 3.44 ± 0.55 cm before treatment was reduced to 2.6 ± 0.36 cm after treatment ($P < 0.05$).

The hormonal changes during GnRHa treatment are shown in Table 3. Serum gonadotropin levels as well as serum estradiol decreased significantly. All women had postmenopausal estradiol levels after 8 weeks of treatment. A slight but significant increase in cholesterol and triglyceride levels was observed after GnRHa treatment,

Table 2
Patient characteristics

Variable	Mean ± S.E.M.	Range
Age (years)	32.26 ± 0.75	24–41
Height (cm)	155.92 ± 0.75	149–168
Weight (kg)	51.21 ± 0.96	41–67
BMI (kg/cm^2)	21.07 ± 0.38	16.80–27.92

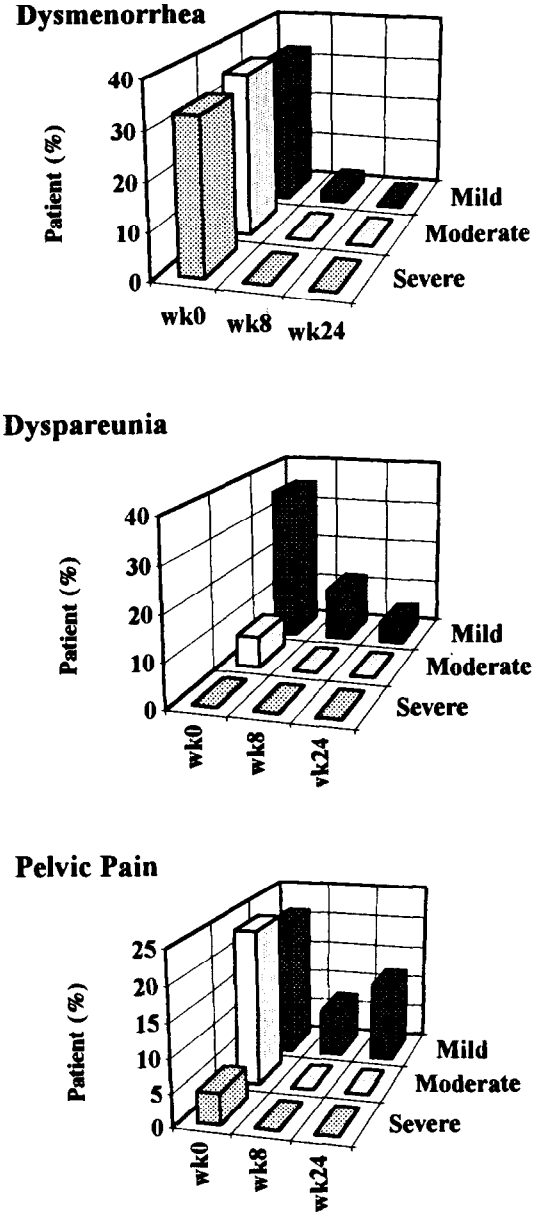

Fig. 1. Pain symptoms during triptorelin treatment.

however all the values were within normal limits. HDL cholesterol increased slightly after treatment but was not statistically significant (Table 4).

BMD was examined by DEXA at the radius, lumbar vertebrae, femoral neck and total body.

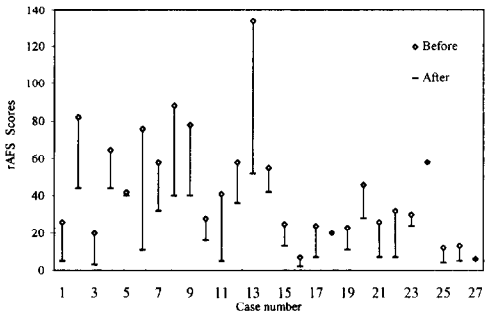

Fig. 2. Laparoscopic assessment (rAFS scores) before and after triptorelin treatment.

Table 3
Hormonal profiles (mean ± S.E.M.) before, during and after triptorelin treatment

Hormone	Week 0	Week 8	Week 24
LH (mIU/ml) ($n = 27$)	8.92 ± 1.62	1.23 ± 0.46*	0.38 ± 0.10*
FSH (mIU/ml) ($n = 28$)	7.34 ± 0.72	4.43 ± 0.39*	5.07 ± 0.38*†
Estradiol (pg/ml) ($n = 40$)	81.94 ± 11.87	14.93 ± 1.78*	17.94 ± 3.44*

*Significant difference from week 0 ($P < 0.001$); †significant difference from week 8 ($P < 0.05$).

After treatment, total BMD as well as BMD of the lumbar vertebrae and femoral neck decreased significantly in most cases. The mean reduction was approximately 3–4%. In some cases a loss of up to 10% of BMD was observed (Fig. 4).

After discontinuation of treatment menses returned 83.76 ± 2.91 days after the last triptorelin injection (Fig. 5). Seventy percent of patients began menstruating within 90 days of the last injection. Two patients conceived spontaneously without prior menses. Their pregnancy tests were positive at 72 and 80 days after the last GnRHa injection.

The adverse effects of triptorelin treatment are shown in Fig. 6. Hot flushes were the most common side effect affecting about 75% of patients. Other common side effects included night sweating, vaginal dryness, headache, dizziness, nausea, insomnia, joint pain and tiredness. Most of the symptoms were tolerable and no treatment was required. All patients were satisfied with this pain-free treatment and judged the treatment favorable.

4. Discussion

The results of this study confirm those of previous studies on the efficacy of GnRHa therapy for endometriosis especially for pain relief [1–5]. The subjective and objective improvements in en-

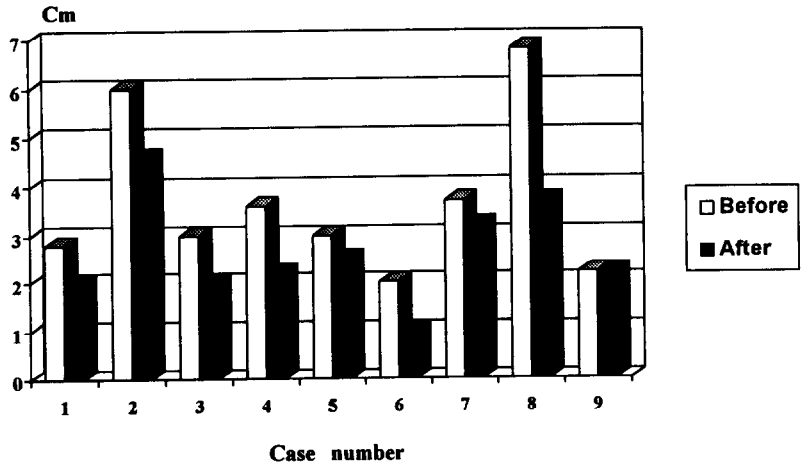

Fig. 3. Size of ovarian endometrioma (cm) before and after triptorelin treatment.

Table 4
Lipid profiles (mean ± S.E.M.) before and after triptorelin treatment ($n = 43$)

Lipid	Before	After
Cholesterol (mmol/l)	4.82 ± 0.14	5.31 ± 0.15**
Triglyceride (mmol/l)	0.96 ± 0.06	1.11 ± 0.07*
HDL cholesterol (mmol/l)	1.35 ± 0.05	1.41 ± 0.05

*$P < 0.05$; **$P < 0.001$.

dometriosis by GnRHa are mediated through its estrogen-lowering effect. Chronic exposure to GnRHa leads to a reduction in gonadotropins and ovarian steroid secretion. After a brief 'flare-up' effect of triptorelin, prolonged suppression of gonadotropins and ovarian steroids remains throughout the treatment period. At 8 weeks of treatment serum LH and FSH were effectively suppressed in all cases and serum estradiol was reduced to postmenopausal levels.

Most patients' symptoms were alleviated within 2 months of commencing medication. Reduction in rAFS scores after 24 weeks of treatment was observed in most cases at all stages of the disease. Improvement in rAFS scores was mostly due to the reduction of endometriotic implants rather than the amount of adhesions. This finding reveals that GnRHa treatment suppresses endometriotic lesions. In some studies a small reduction in adhesion scores has been observed [7,8]. However, it has been shown that shortly after discontinuation of GnRHa the pathology will recur in most cases [9].

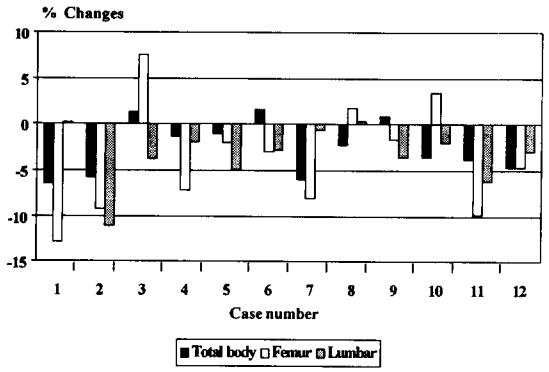

Fig. 4. Percentage changes in BMD after 24 weeks of triptorelin treatment.

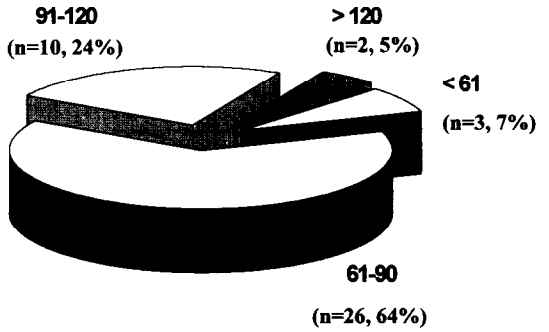

Fig. 5. Resumption of menses after triptorelin treatment (days from last injection).

The size of ovarian endometrioma was reduced in eight out of nine patients. Medical treatment of endometrioma has usually been considered ineffective. However, with GnRHa treatment, a decrease in the size of ovarian endometrioma, ranging from 39 to 82%, has been observed in several studies [1,4,10]. Recent studies have shown that 3 months' treatment with GnRHa is effective in reducing the size of some ovarian endometriomas. A greater than 25% reduction in diameter has been observed in about 80% of patients receiving GnRHa [11]. The possible advantages are prevention of endometriotic cyst rupture while awaiting surgery and preoperative reduction of pathology, which may ease the operation especially if laparoscopy is to be performed.

In this study a slight increase in serum cholesterol and triglyceride was observed, but there was no significant change in HDL cholesterol, which is in accordance with the results of other studies [3,4]. These small lipoprotein changes are unlikely to increase the atherogenic potential since the values are still within the normal range. Studies on the subfraction of lipoprotein have revealed no significant changes during 6 months of GnRHa therapy [4]. These minor changes in serum cholesterol and triglyceride may relate to the hypoestrogenic effect of GnRHa treatment.

This study has confirmed the findings of previous studies that prolonged GnRHa treatment can reduce BMD [4,12,13]. There are several methods of BMD measurement. DEXA was used in the present study, revealing a bone loss of about

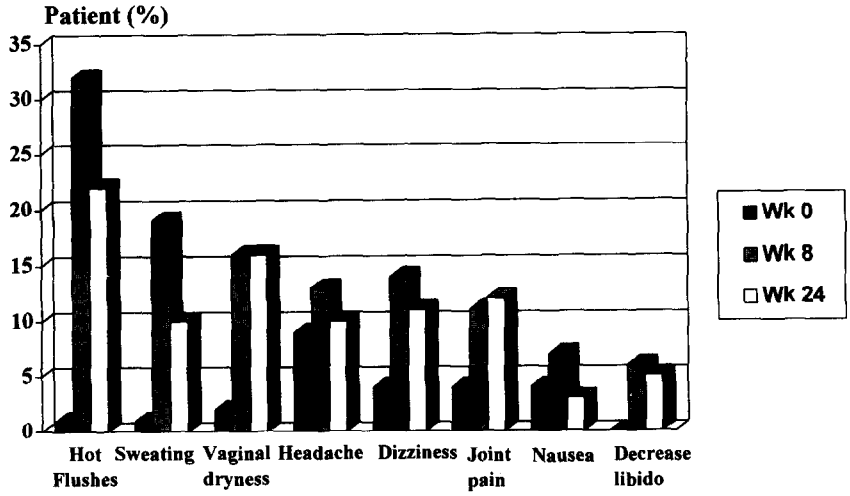

Fig. 6. Adverse effects of triptorelin treatment.

3 and 4% at the lumbar vertebrae and femoral neck, respectively. In the initial report, after 6 months of treatment, BMD at the lumbar site decreased by about 5.6%. In other studies, BMD loss after GnRHa treatment was about 5–6% at the lumbar site [12] and 3–4% at the femoral neck [4,13]. It is well known that prolonged hypoestrogenemia will reduce BMD as in the natural menopause. However, in some cases, GnRHa induced more BMD reduction than would occur naturally in the early menopause. After GnRHa treatment most patients recover BMD, however in some patients the recovery is incomplete [14,15]. For safety purposes, at present it is advocated to use GnRHa continuously for no more than a period of 6 months [16]. The adverse effects of prolonged GnRHa treatment on BMD may be harmful, especially in patients who already have low BMD and who have undergone repeated courses of GnRHa treatment. The cumulative bone loss may increase osteoporosis later in life due to the low peak bone mass on entering the menopause. For this reason 'add back' therapy may be considered [4,16]. There are currently several 'add back' regimens which can retard or prevent the bone loss effect of GnRHa [4,16–19]. Another strategy to decrease the GnRHa effect on bone mass is a shorter course of treatment. A 3-month GnRHa regimen has been shown to be effective in the treatment of endometriosis [10].

Most adverse effects of GnRHa therapy in this study were the result of hypoestrogenemia. Before treatment the patients should be informed of these common effects. Most symptoms that occurred were mild and needed no specific treatment. In severe cases 'add back' therapy with low-dose estrogen or tibolone should be considered [16–19]. After discontinuation of triptorelin most patients resumed their menses within 90 days of the last injection. The data confirmed the results of a previous study [2]. This rapid return of ovarian function is beneficial to infertile couples. Some patients may become pregnant by their first ovulatory cycle.

GnRHa can be administered by several routes except orally due to the rapid degradation of enzymes in the digestive tract [1]. Since endometriosis usually requires prolonged treatment, the long-acting preparation may have several advantages over the short-acting formulation. Triptorelin is available in microparticulate suspensions for monthly intramuscular injection. A single dose of 3.75 mg will deliver a daily dose of 100 μg of GnRH for 30 days. Depot preparations usually produce more rapid and complete suppression of ovarian function than short-acting drugs [4]. Monthly injection is more convenient for the patient and ensures better compliance. At the beginning of this study triptorelin was the only long-acting GnRHa available in Thailand, thus we were un-

able to make comparisons with other GnRHa preparations.

In conclusion, this study demonstrates the efficacy of long-acting triptorelin for the treatment of endometriosis. It effectively suppressed gonadotropins and estrogen secretion. Both subjective and objective improvements were achieved during treatment in most patients. Most side effects of GnRHa were due to a hypoestrogenic state and were usually mild and needed no specific treatment. However, the decrease in BMD during treatment may be harmful and preventive strategies should be considered.

Acknowledgments

This study was kindly supported by Ferring, Malmö, Sweden.

References

[1] Erickson LD, Ory SJ. GnRH analogues in the treatment of endometriosis. Obstet Gynecol Clin North Am 1989; 16: 123-143.

[2] Zorn J-R, Comaru-Schally AM, Mathieson J, Schally AV, Risquez F. Treatment of endometriosis with a delayed release preparation of the agonist D-Trp^6-luteinizing hormone-releasing hormone: long-term follow-up in a series of 50 patients. Fertil Steril 1990; 53: 401-406.

[3] Dlugi AM, Miller JD, Knittle J. Lupron depot (leuprolide acetate for depot suspension) in the treatment of endometriosis: a randomized, placebo controlled, double blind study. Fertil Steril 1990; 54: 419-427.

[4] Shaw RW. Evaluation of treatment with gonadotrophin-releasing hormone analogues. In: Shaw RW, editor. Endometriosis, current understanding and management. Glasgow: Bell and Bain, 1995: 206-234.

[5] Meldrum DR, Chang RJ, Lu J, Vale W, Rivier J, Judd HL. Medical oophorectomy using a long-acting GnRH agonist: a possible new approach to the treatment of endometriosis. J Clin Endocrinol Metab 1982; 54: 1081-1083.

[6] American Fertility Society. Revised American Fertility Society classification of endometriosis. Fertil Steril 1985; 43: 351-352.

[7] Henzl MR, Corson SL, Moghissi K, Buttram VC, Berquist C, Jacobson J. Administration of nasal nafarelin as compared with oral danazol for endometriosis. N Engl J Med 1988; 318: 485-489.

[8] Shaw RW. An open randomised comparative study of the effect of goserelin and danazol in the treatment of endometriosis. Fertil Steril 1992; 58: 265-272.

[9] Ever JLH. The second look laparoscopy for evaluation of the result of medical treatment of endometriosis should not be performed during ovarian suppression. Fertil Steril 1987; 47: 520-523.

[10] Wright S, Valdes CT, Dunn RC, Franklin RR. Short-term Lupron and danazol therapy for pelvic endometriosis. Fertil Steril 1995; 63: 504-507.

[11] Donnez J, Nisolle M, Clerckx F. Evaluation of preoperative use of danazol, gestrinone, lynestrenol, buserelin spray and buserelin implant in the treatment of endometriosis associated infertility. In: Chandha DR, Buttram VC Jr, editors. Current concepts in endometriosis. New York: Liss, 1990: 357-382.

[12] Matta WH, Shaw RW, Hesp R, Katz D. Hypogonadism induced by luteinizing hormone-releasing hormone agonist analogues: effects on bone density in premenopausal women. Br Med J 1987; 294: 1523-1524.

[13] Uemura T, Suzuki N, Mohri J, Katagiri N, Osada H, Minaguchi H. Effect of gonadotropin-releasing hormone agonist on the bone mineral obesity of patients with endometriosis. Fertil Steril 1994; 62: 246-250.

[14] Waibel-Treber S, Minne HW, Scharla SH, Bremen TH, Ziegler RZ, Leyendecker GL. Reversible bone loss in women treated with GnRH agonist for endometriosis and uterine leiomyoma. Hum Reprod 1989; 4: 384-388.

[15] Dawood MY, Ramos J, Khan-Dawood F. Depot leuprolide acetate versus danazol for treatment of pelvic endometriosis: changes in vertebral bone mass and serum estradiol and calcitonin. Fertil Steril 1995; 63: 1177-1183.

[16] Surrey ES. Steroidal and nonsteroidal 'add-back' therapy: extending safety and efficacy of gonadotropin-releasing hormone agonists in the gynecologic patient. Fertil Steril 1995; 64: 474-481.

[17] Edmonds DK, Howell R. Can hormone replacement therapy be used during medical therapy of endometriosis? Br J Obstet Gynaecol 1994; 101 Suppl 10: 24-26.

[18] Lindsay P, Shaw RW. The effect of Livial on GnRH agonist induced bone loss [abstract]. 7th International Congress on the Menopause: 1993 June 20–24; Stockholm.

[19] Howell R, Edmonds DK, Dowsett M, Crook D, Lees B, Stevenson JC. Gonadotropin-releasing hormone analogue (goserelin) plus hormone replacement therapy for the treatment of endometriosis: a randomized controlled trial. Fertil Steril 1995; 64: 474-481.