

Pre-surgical treatment of uterine myomas with LH-RH agonists

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Summary: Twenty-five non-menopausal women with uterine myomas were treated with LHRH-analogues for 3-6 months. An average reduction of 40% in uterine volume was observed. One patient refused to complete her therapy, three had no more menses after the interruption of treatment, nine underwent myomectomy within four weeks of their final administration, while in 12 cases hysterectomy was performed. In all cases the decrease in uterine volume induced by the analogue allowed a more limited intervention and prevented excessive blood loss.

Key words: LH-RH agonists; Uterine myomas; Surgery.

INTRODUCTION

Uterine leiomyomas represent the most common benign tumors of the female genital tract; they occur in 20%-25% of all women of reproductive age ^(1,2). They are often associated with low abdominal pain, abnormal uterine bleeding, recurrent abortions, premature labour or rupture of the membranes, abnormal presentation or placentation ⁽³⁾; they still represent the most common indication for hysterectomy ^(4,5).

Several studies indicate that leiomyomas are estrogen-sensitive ^(6,7). High estrogen states are associated with their growth and it is well known that they shrink in menopause, when serum estrogen levels are physiologically low ⁽⁸⁾.

Lumdens, et al. ⁽⁹⁾ reported a higher concentration of estrogen receptors in uterine leiomyomas (70 fm/mg of proteins) than in normal myometrium (30 fm/mg of proteins). The concentration of estrogen receptors in leiomyomas changes during the menstrual cycle with the changes in serum estradiol ⁽¹⁰⁾.

The suppression of ovarian estrogens by Luteinizing Hormone-Releasing Hormone agonists (LHRH-a) has been recently introduced in the treatment of uterine myomas ^(11,12,13). Chronic administration of highly potent LHRH analogues results in pituitary desensitization and «down regulation» of receptors and inhibition of gonadotropin secretion, thus inducing a state of hypogonadism ⁽¹⁴⁾. The estradiol-lowering effect of LHRH-a is completely reversible and, following cessation of therapy, a rapid resumption of gonadal activity is observed ⁽⁴⁾.

Several studies reported a reduction in the size of uterine myomas after LHRH-analogue treatment: several Authors have demonstrated a decrease in uterine volume of 10% to 70%, according to the different analogues and the different pat-

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terms of administration they used (^{4, 7, 11, 12, 13}).

The rapid reduction in uterine volume at the beginning of treatment may be due to a considerable lowering of blood flow. Hofmann, et al. (¹⁵) found that Epidermal Growth Factor (EGF) receptors decrease in myomas (but not in normal myometrium) during treatment with LHRH-a; therefore EGF may be involved in the shrinkage of myomas induced by hypoeostrogenism.

MATERIALS AND METHODS

Between January 1988 and May 1991, 25 non-menopausal patients aged from 23 to 55, with one or more uterine myomas, were included in the study. Six of them were treated with nasal Buserelin three times a day, five with monthly intramuscular administration of Leuprolide Acetate (Enantone) and the remaining 14 were given a delayed-release microcapsule preparation of D-Trp-6-LHRH (Decapeptyl) injected intramuscularly every 28 days.

Nine patients (Group 1) were treated with LHRH-analogues (2 with Buserelin, 2 with Enantone and 5 with Decapeptyl) for three months (« short term » therapy), then underwent myomectomy within 4 weeks of their final administration. A second group of 16 patients was treated with LHRH-a (4 with Buserelin, 3 with Enantone and 9 with Decapeptyl) for six months (« long term » therapy) (tab. 1).

TABLE 1. - *Patients treated with LHRH-analogues.*

SHORT-TERM THERAPY (3 months)			
No. of patients	LHRH-a	Route	Frequency
2	Buserelin	nasal	daily
2	Enantone	i.m.	monthly
5	Decapeptyl	i.m.	monthly
Total	9		
LONG-TERM THERAPY (6 months)			
No. of patients	LHRH-a	Route	Frequency
4	Buserelin	nasal	daily
3	Enantone	i.m.	monthly
9	Decapeptyl	i.m.	monthly
Total	16		

FSH, LH and Estradiol were measured monthly, starting before the first injection, using standard laboratory methods.

Volumes of uterus and myomas were measured by ultrasonographic examination before, during and after treatment. Uterine volumes were calculated by a formula for ellipsoid tumors: $4/3\pi R1 R2 R3$, where R1, R2 and R3 were the radii of each of the three uterine dimensions. Myomas were considered as ellipsoid tumors, as well.

RESULTS

In all the 25 patients we observed a mean reduction in uterine volume of about 40% (range 25%-68%). The most rapid shrinkage in uterine volume was found after the first month of treatment (fig. 1, 2).

Mean volume of the myomas decreased by about 45%, the reduction being greater than 50% in 10 cases (fig. 3).

Before treatment, in the early follicular phase, the average basal levels of FSH and LH were 4.2 mIU/ml (range 2.4-5.9) and 6.5 mIU/ml (range 2.8-8.8), respectively. The mean E2 level was 81 pg/ml (range 15-128).

FSH fell rapidly to very low levels (below 2.5 mIU/ml), while LH levels dropped less rapidly: within 30 days the average level was 3.2 mIU/ml and it remained low for the whole treatment period. Estradiol levels decreased within 4 weeks to post-menopausal levels (below 30 pg/ml) in all patients and remained at such levels till the end of therapy.

Two patients in Group 1 become pregnant after medical and surgical treatment.

One of the 16 patients in Group 2 refused to complete her therapy because of severe headaches, 3 of them had no more menses after the interruption of treatment, 4 underwent vaginal hysterectomy, while in 8 cases abdominal hysterectomy was performed.

In all cases the decrease in uterine volume induced by the analogue allowed a

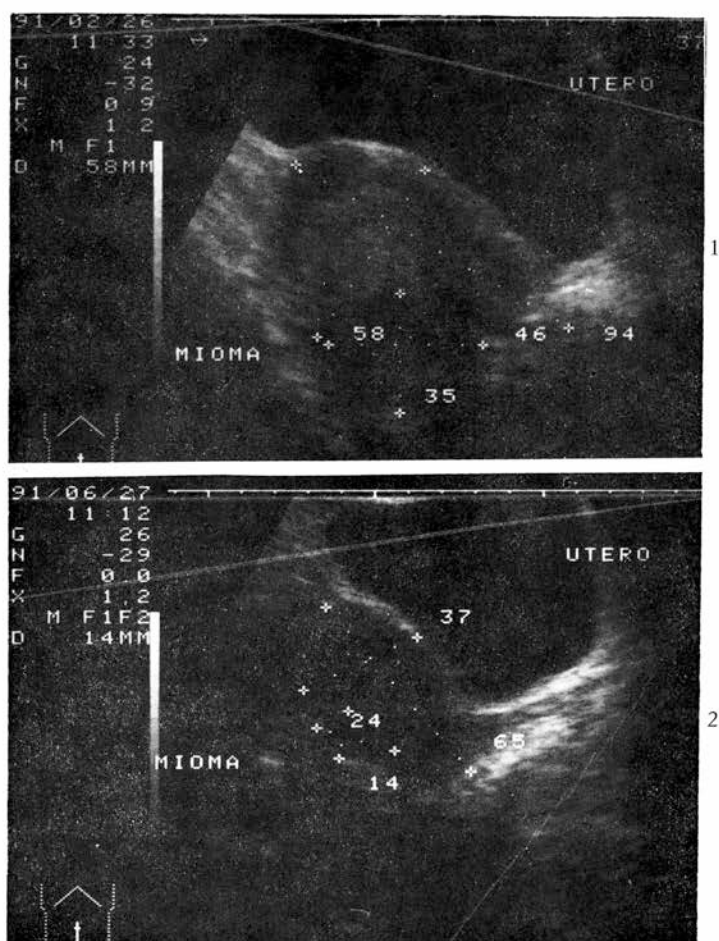


Fig. 1,2. — Shrinkage in uterine volume in a 36-year-old patient before and after three months of medical treatment (confirmed by ultrasonographic examination).

more limited surgical intervention and prevented excessive blood loss.

Side effects were few and well tolerated, except in one case.

Twenty-three patients experienced hot flushes during treatment; intermittent vaginal bleeding was present in 8 cases and 15 patients experienced vaginal dryness and dyspareunia. Other side effects included headaches and backaches. All the side effects disappeared within 5 weeks after the end of treatment.

DISCUSSION

In the present study both nasal (Buserelin) and intramuscular (Enantone and Decapeptyl) treatment produced an improvement in the symptoms and a decrease in uterine volume and in the size of myomas.

Intramuscular therapy seems to be the more convenient, as only one injection is required every 4 weeks.

It is well known that in most cases uterine volume increases after the end of

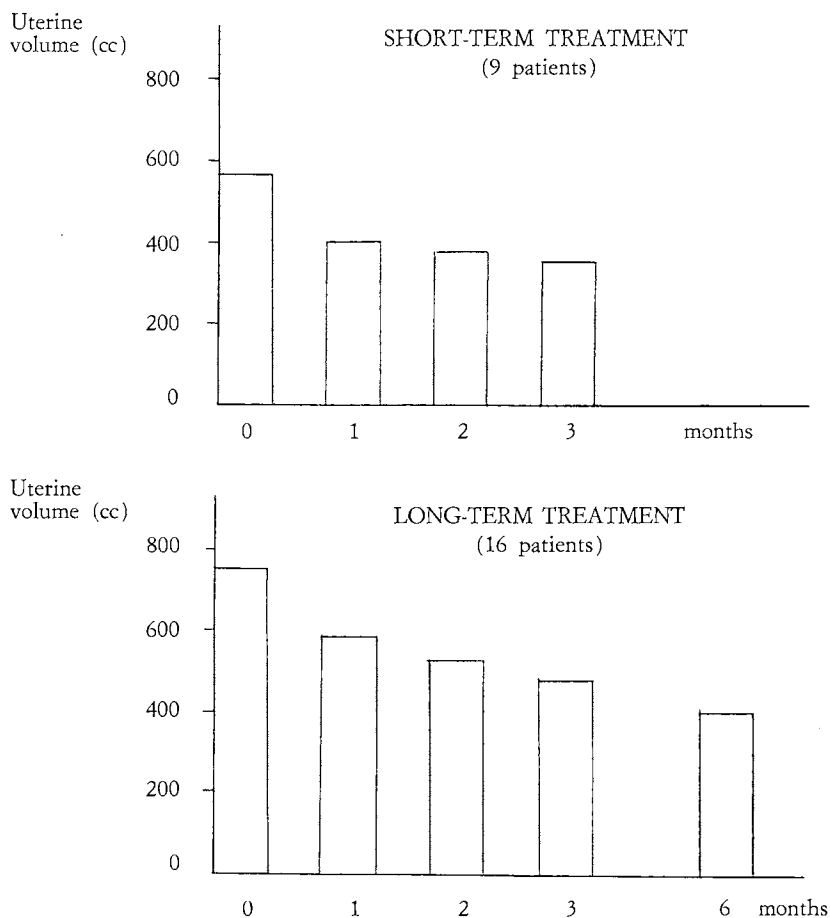


Fig. 3. — Mean uterine volume during treatment with LHRH - anal.

medical treatment. This finding suggests that these agents are unlikely to be used as definitive medical therapy for leiomyomas, except in premenopausal women with symptomatic myomas, who wish to avoid surgery, until natural menopause occurs.

In younger women a three-month (« short-term ») or six-month (« long-term ») treatment can be given before myomectomy or hysterectomy. Pre-surgical treatment with LHRH-a allows better operative conditions, making surgery technically easier, with decreased

blood loss and diminished risk of post-operative complications. In fact medical treatment induces a reduction in myometrial thickness and in uterine vascularization; so a more limited operation can be performed, with a smaller uterine scar and more possibilities of future pregnancies.

Besides, since pre-operative anemia increases the risk of intra- or post-operative blood transfusion, pre-surgical treatment with LHRH-a may induce amenorrhea and help to restore hemoglobin concentration to normal levels, in women with menorrhagia-induced anemia.

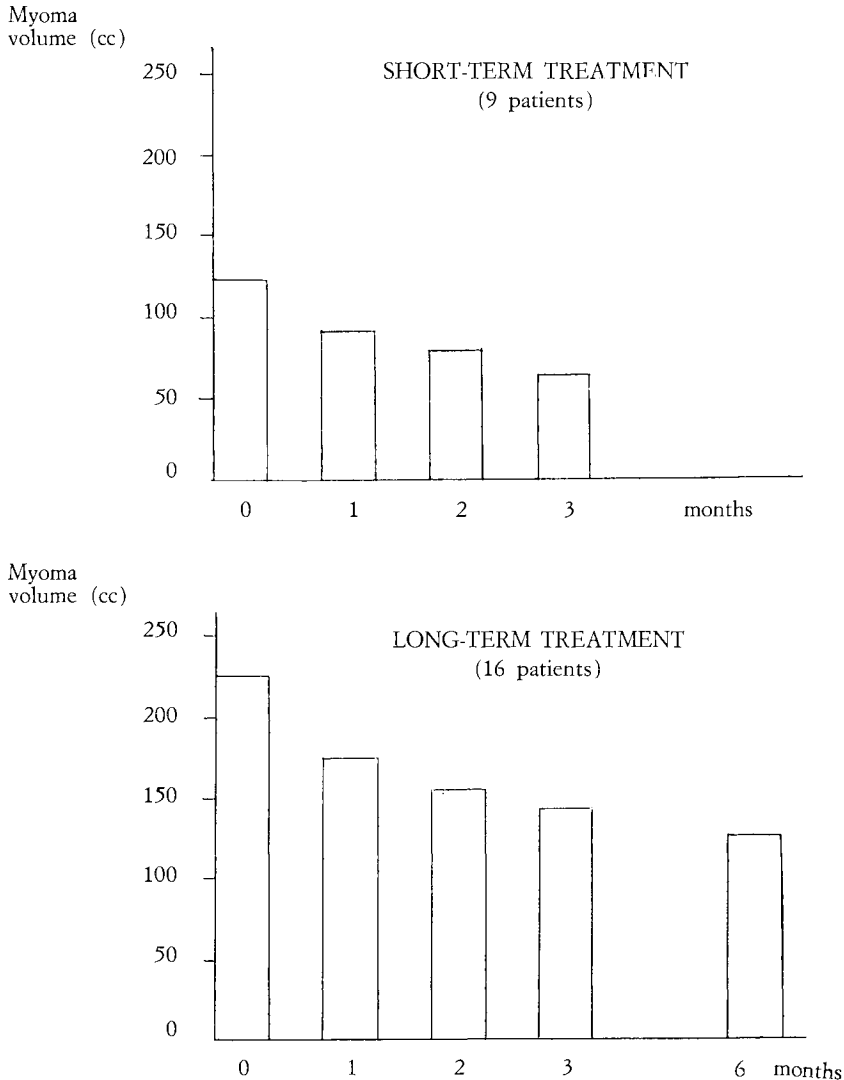


Fig. 4. — Mean total myoma volume during treatment with LHRH - anal.

However, the shrinking effect of the analogue may increase the risk of post-operative relapses, since very small myomas cannot be noticed during myomectomy.

Most of the observed side effects were mild and related to reversible estrogen inhibition.

As regards the effects of LHRH-a on bone metabolism and the risk of osteoporosis, Leusden, et al. (7) found that serum calcium, phosphate, alkaline phosphatase and osteocalcin increases during treatment, but calcium and hydroxyproline excretion remains unaltered, suggesting that an increased bone turnover

rather than bone loss occurs. However, some Authors suggest adding low doses of progestins ⁽¹⁶⁾ and/or conjugate estrogens ⁽³⁾ to reduce demineralization and menopausal symptoms.

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