The management of leiomyoma uteri by GnRH analogues

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Summary: Therapy with GnRH analogs is the first medical solution to be really effective in treating uterine fibromas, even if with limited and temporary benefits. Out of the 12 patients treated the Authors observed that a 60% reduction of the volume of the uterus can be achieved after 3-6 months therapy, with rapid recuperation of the initial volume after interruption of the treatment. It is therefore preferable to use GnRH analogs as a propedeutic therapy rather than surgery.

INTRODUCTION

Leiomyomata or fibroleiomyomata uteri are the most common types of pelvic tumor affecting the female sex ([1, 2]). They attack approximately 25 fertile women out of 100, though they are more frequent in women over 35 ([3, 4]). The most frequent symptoms are menorrhagia and pelvic pains.

They sometimes affect the reproductive mechanisms very seriously, threatening abortion, habitual abortion, premature delivery, mechanical and dynamic dystociae.

In a condition of hypoestrogenism, such as the menopause, the volume of fibromata is reduced, so that treating them with GnRH agonists has been suggested. Since 1983 Filicori and colleagues ([5]) have been demonstrating that it is possible to obtain a remarkable reduction of fibromata after three months of therapy. Many other researchers have corroborated these conclusions and added further considerations ([6, 10]).

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MATERIALS AND METHODS

We evaluated a group of patients aged from 31 to 49 years (mean age 42), all affected by fibromyoma uteri. Clinical diagnosis was always completed with *ultrasonography*, so as to determine the exact dimension of the neo-formations and to obtain documentation useful for later comparison. All patients underwent hematic assays, including, FSH, LH, 17-β-estradiol, hemochrome; iron and ferritin concentrations were also checked. Before treatment the patients were informed of the possibility that the success of the therapy might be only partial. Bone density was measured on the 10′ distal of the non-dominating limb radius. Hematic and hormonal assays were performed after three, and then after six months of therapy. When the treatment was over, bone density was measured again.

Among GnRH analogues we chose Depot Goserelin (3.6 mg) which we administered subcutaneously every four weeks for a least six months. The beginning of treatment coincided with the start of a menstruation.

Table 1. – *Monitoring of treatment with GnRH agonists.*

Initial values of Estradiol, LH, FSH.
Gynecologic examinations, gynecologic anamneses.
Checking of Estradiol and LH after 1-2 months from the beginning of treatment.
Specific examination for the steroid-dependent diseases that are being treated (e.g. echography for myomas, plasmatic testosterone for hyper-androgenism).
Densitometric assay at the beginning and after six months.
In the absence of menstruation after 3 months from the end of the therapy dosage of FSH and HCG.

RESULTS

The reduction of 17-β-estradiol levels turned out to be very remarkable and lasting during the treatment. It was rapidly reduced from 150 pg/ml and steadied around 30. Similarly, LH levels which were initially around 40 mIU/ml rapidly decreased below 10 mIU/ml throughout the treatment. The above-mentioned hormones can therefore be useful for monitoring the therapy; on the contrary, FSH was fluctuating and diminished less: in our patients it was from around 20 mIU/ml to 12 mIU/ml approximately. As already mentioned above, the size of fibromata was measured by means of ultrasonography before treatment, and then after three and six months of therapy. We observed in all patients a significant regression in the volume of fibromata.

The most remarkable therapeutical effect, however, was noted by the third month of therapy, when approximately 90% of global reduction had already taken place. Mean diminution steadied around 70% with respect to initial size (Tables 1, 2).

From the third month onwards the further regression of the mass of the fibroma did not exceed 10%. Global reduction of the size of the fibromata was,

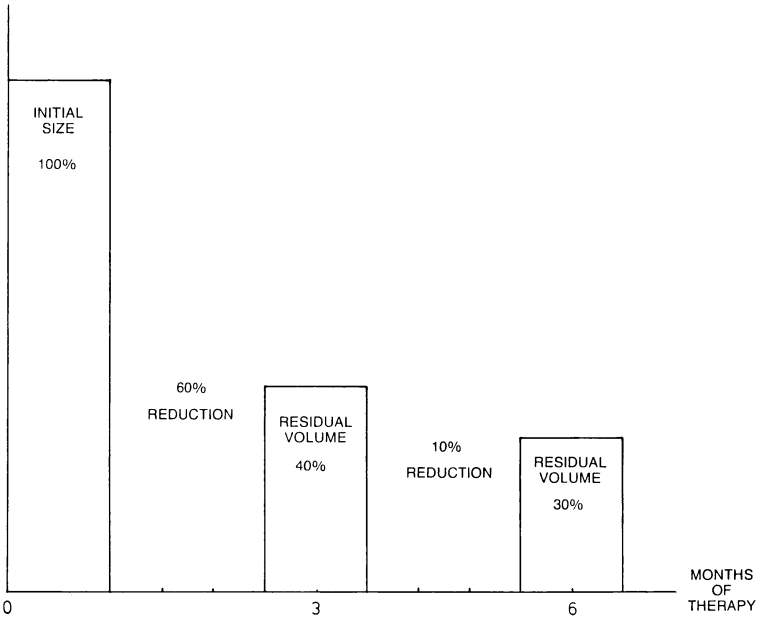


Fig. 1. — Variations in the size of fibromata.

Table 2. – *Effects of treatment with GnRH agonists.*

Amenorrhoea.
Hot flushes.
Irregular vaginal hematic losses.
Vaginal dryness / Dyspareunia.
Decline of libido.
Osteoporosis.
Headache.
Depression.
Insonnia.
Weight increase/loss.
Arthralgia / Myalgia.
Hair loss.
Peripheric edema.

nevertheless, always statistically significant ($p<0.01$). During the treatment symptoms ascribable to hypoestrogenism (Table 2) were noted: hot flushes, at times very intense, in five cases, vaginal dryness in three cases, neurological symptoms (anxiety, sleeplessness, irritability, headaches) in four cases. None of the patients showed a tendency to develop osteoporosis. In the three cases which had manifested this tendency we made a further investigation by measuring bone density with dual photon absorptiometry on the spine at L_2 and L_4, so that all doubts were definitely dispelled. A very interesting datum regards lyposideremic anemia, which affected eight patients out of twelve. At the outset mean hemoglobin level was 10.2 mg/100 ml (with a minimum if 8.3 mg/100 ml), while after three months of therapy it reached 12.1 mg/100 ml, thanks to an addition of supplementary Proteinsuccinylate Iron (*) administered orally for a period of three months. Finally, it must be pointed out that we observed bothersome spotting in only one case in which FSH and 17-β-estradiol were not low enough, so that it was necessary to temporarily administer intranasal buserelin (**) at a dosage of 400 μ g/die each spray being 100 μ g; buserelin had to be given twice daily.

It must also be observed that seven patients asked to continue the therapy beyond the fixed duration, considering the improvement it had effected in their lives and also in order to further improve the results achieved through the therapy: restoration of the condition which preceded the fibroma in a relatively short time is, indeed, a very plausible hypothesis.

DISCUSSION

The therapy with GnRH analogue agonists has proved to be the first really successful medical solution to fibromyomata uteri. Undoubtedly it cannot be strictly considered an alternative to surgical therapy, but it can be a proper method of preparation for patients who might need surgical therapy at a later time.

In evidence of this is the correction of anemiae, which makes it possible to avoid blood transfusions during surgical operation. It has been estimated that the risk of blood transfusion essential to patients who undergo hysterectomy or myomectomy is strictly related to the level of preoperative anemia ([11]).

It has often been pointed out that not all fibromyomata respond to treatment in the same way; this is due to the fact that fibromyomata are heterogeneous neo-formations and that the greater the fibrose component is the less significant the response to hypoestrogenism.

In any case, the reduction in the size of a fibromatous uterus ranges from 38% to 61% after three or six months of therapy ([8–12]) (Table 3). In our patients too we noticed a significant reduction of the fibromatous mass.

Among the side effects provoked by hypoestrogenism, which perfectly corre-

(*) Pernexin 40 - Schering

(**) Suprefact - Hoeckst

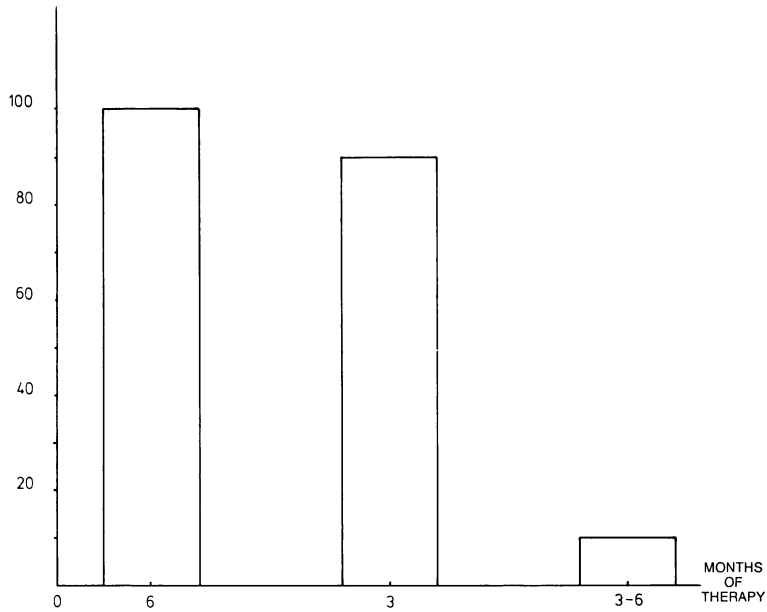
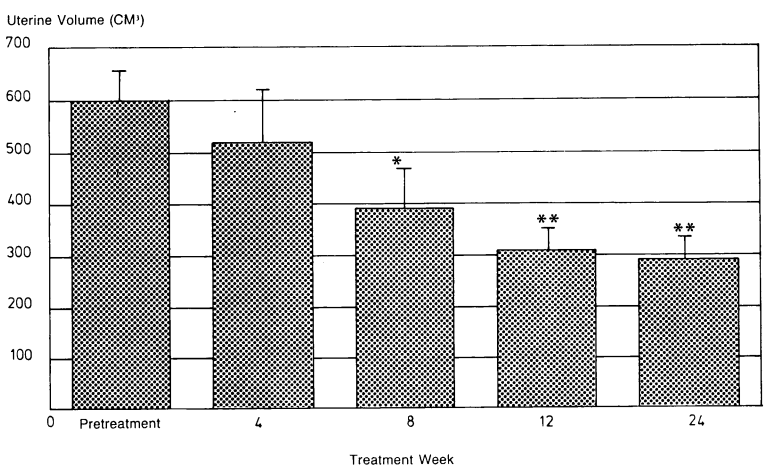


Fig. 2. — Size of fibromata: rate of reduction.



■ Leuprolide plus Placebo.

* $p < 0.05$ compared with pretreatment
** $p < O0.01$ compared with pretreatment

Fig. 3. — Reduction of uterine volume in the course of treatment with Leuprolide (Friedman A. J., Barbieri R. L., 1988).

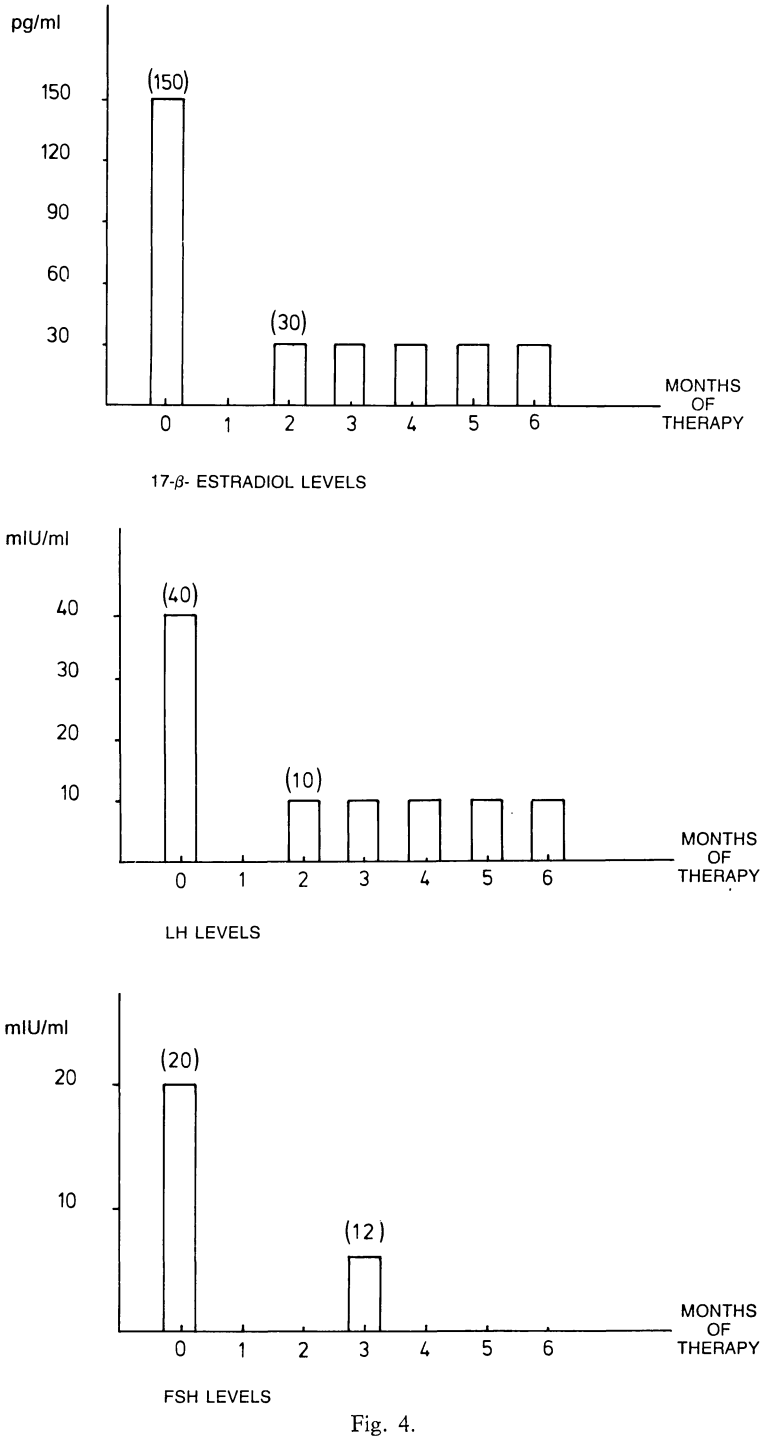

pg/ml
150
120
90
60
30
(150)
(30)
0 1 2 3 4 5 6
MONTHS OF THERAPY
17-β- ESTRADIOL LEVELS
mIU/ml
40
30
20
10
(40)
(10)
0 1 2 3 4 5 6
MONTHS OF THERAPY
LH LEVELS
mIU/ml
20
10
(20)
(12)
0 1 2 3 4 5 6
MONTHS OF THERAPY
FSH LEVELS

Fig. 4.

spond to those related to the menopause, hot flushes were noted during treatment with GnRH analogues too. The addition of medroxyprogesterone acetate (MAP) antagonizes the hot flushes [13] but renders the treatment for the reduction of uterine volume [14] less effective. The addition of MAP [15] or norethindrone [16] also counteracts the loss of bone tissue. The problem consists, then, in balancing the GnRH agonists' therapeutical effects (reduction of fibroma, endometriosis, etc.) and the side effects of hypoestrogenism (hot flushes, demineralization, etc.). It has been demonstrated that a concentration of 20 pg/ml of estradiol can considerably reduce the size of uterine fibroids, but it involves the most unpleasant and dangerous side effects of hypoestrogenism. With a level of 40 pg/ml (obtained, for example, by adding conjugate estrogens to GnRH agonists) it is possible to reduce demineralization and menopausal symptoms without having the fibromyoma back to initial size.

The long-term care is still being evaluated and it is not yet possible to perform it on a larger scale. Friedman's and Barbieri's conclusions, then, remain valid [8]: anemia and surgical risks linked to fibromyomata are still serious gynecological problems. In order to achieve the best results, a combination of medical and surgical therapies can be suggested. Before performing hysterectomy or myomectomy, a three or six month's therapy aiming at a reduction of 50-60% of uterine size [4–10, 14–15, 71–18] is very useful; in this way surgical traumatism will be reduced (possibility of performing Pfannestiel's incision or even vaginal hysterectomy, diminution of bleeding due to reduction of the myoma's vascularization [12] and thus less frequent necessity for performing blood transfusions).

To conclude, we can affirm that GnRH agonists represent a real innovation in the treatment of fibromyoma uteri and can be an effective means for treating these uterine neo-formations more and more adequately. Under this aspect, it must be pointed out that controlled research on a greater number of cases will make it possible to define more precisely the real therapeutical possibilities of these drugs, and to determine their directions more and more definitely.

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