

Uterine fibroids: protocols of integrated medical/surgical treatment

U. MONTEMAGNO - G. DE PLACIDO - N. COLACURCI
F. ZULLO - M. LOCCI

Summary: Uterine fibroids are the most common solid pelvic tumor in women and in these last years their management has been deeply reviewed. An optimal integration of GnRH analogue treatment with different surgical techniques require an adequate work-up for the specific problems of each single patient. For a correct management of these patients, we divided them into 4 categories on the basis of symptoms and specific objectives to pursue: a) perimenopausal patients; b) young patients, symptomatic or with large myomas, with no wish for more children; c) young patients, symptomatic or with large myomas, wishing to preserve fertility; d) infertile patients or patients with history of repeated miscarriages.

Our suggested work-up is the following: a careful USGraphic evaluation of fibroid size and localization, a transvaginal doppler examination of the uterine blood supply, a complete haematochemical analysis, a hysteroscopy guided biopsy and a complete bone evaluation. On the basis of the above mentioned evaluations for each group we will use a different therapeutic approach in regard of either length of medical treatment (for three to six months, for one or more cycles) or necessity of surgical treatment (with the possibility to get a natural menopause), or different surgical techniques (operative hysteroscopy and/or laparoscopy, laparotomic myomectomy, vaginal or abdominal hysterectomy).

Key words: Uterine fibroids; Medical treatment; Surgical treatment.

INTRODUCTION

Uterine fibroids are the most common organ disease in gynaecology, affecting 1 woman in childbearing age out of 4.

Until recently there was no other treatment for this disease but surgery, conservative when possible, otherwise radical.

The introduction into the market of drugs such as GnRH analogues, capable of inducing reversible medical menopause,

made medical treatment possible for all the diseases associated with high oestrogen plasma levels, particularly for uterine fibroids.

Since 1983 a number of trials has highlighted the role and efficacy of GnRH analogues in the treatment of uterine fibroids, which have generally undergone a marked and significant reduction in volume (over 40%), though these changes were usually transient, the majority of cases returning to their initial conditions within 3 to 6 months from therapy discontinuation.

Moreover, pretreatment with GnRH analogues usually makes the surgical procedure markedly easier, with a reduction in intraoperative blood loss and a prompt

Gynaecology and Obstetrics Dept I
II Faculty of Medicine and Surgery
"Federico II" University
Naples (Italy)

All rights reserved — No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, nor any information storage and retrieval system without written permission from the copyright owner.

ter postoperative recovery. Also, by inducing amenorrhea, this pretreatment improves the anaemia due to menometrorrhagia, making autotransfusions possible and reducing the risk of non-autologous transfusions (6).

As a result, the cure of uterine fibroids no longer lies exclusively in the hands of surgeons, but requires integrated medical/surgical treatment protocols which can be designed only after a precise evaluation of each individual case.

CLINICAL EXPERIENCES

At present, a fundamental role is played by the refinement in diagnostic procedures achieved with the introduction of transvaginal ultrasonography, flow indices of uterine and myoma vessels – extremely sensitive to hyperoestrinism – and hysteroscopy, which enables us to define exactly the characteristics of fibroids, their pathophysiological aspects and their relation to the reproductive capacity.

It is useful to establish a therapeutic protocol for patients affected by myomatosis, based on the following parameters: patient's age; wish for children; symptoms; site, volume and number of myomas. We may then divide the patients to be treated into 4 categories:

- A) perimenopausal patients;
- B) young patients, symptomatic or with large myomas (uterus > 14th week of pregnancy), with no wish for more children;
- C) young patients, symptomatic or with large myomas, wishing to preserve fertility;
- D) infertile patients or patients with history of repeated miscarriages.

The symptom-free patients in the first two groups are not treated but only followed up, undergoing ultrasonography and Doppler flow measurement every 6 to 12

months; in case of rapid growth in myoma size or significant changes in flow indexes, they will be considered as symptomatic and will thus be included in the proper groups. In our Institution, over the past 5 years, perimenopausal patients have been the most numerous by far among women affected by uterine fibroids (see Fig. 1); this group of patients is most likely to reap greater benefit from the introduction of these new drugs.

Group A (Perimenopausal Patients).

Perimenopausal patients account for 68% of our cases and the treatment of this population is aimed at eliminating menometrorrhagia and reducing pressure symptoms by medical therapy, so that the patients can reach their natural menopause in a state of well-being.

To this purpose we employed GnRH analogues in a cyclic treatment.

The following patients were excluded from this protocol:

- a) patients with ultrasound changes, consisting of an excessive calcification of the myoma fibrous internal structure;
- b) patients who do not show the typical decrease in Doppler flow indices (PI and RI) due to increased flow in uterine arteries and in myoma newly formed vessels, as is the case for example, of in toto fibromatous uterus with diffused micronodules (< 1 cm);
- c) patients with associated ovarian disease or endometrial atypical hyperplasia.

RESULTS

The simple hyperplasia, which is generally present in the areas of the endometrium surrounding the myoma, is not a contraindication to treatment with GnRH analogues, deriving great benefit from this therapy, as was also shown by our experience in women with menometrorrhagia

UTERINE FIBROIDS
Years 1986-1991 - Cases n. 315

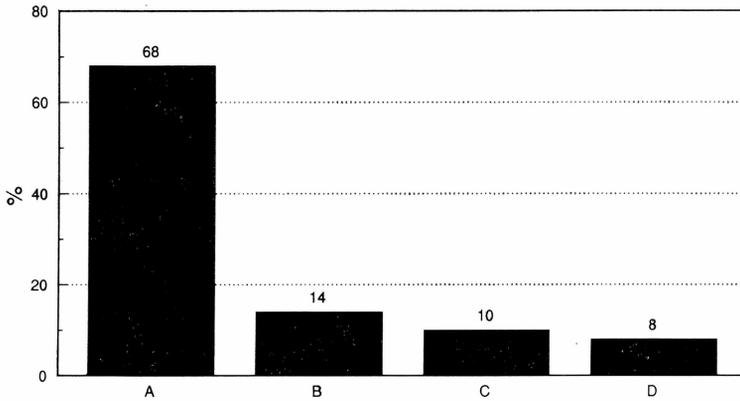


Fig. 1. — % cases of uterine fibroids at the Dept. of Obstetrics and Gynecology I of the University Federico II, Naples: A) perimenopausal patients; B) young patients, symptomatic or with large myomas (uterus > 14th week of pregnancy), with no wish for more children; C) young patients, symptomatic or with large myomas; wishing to preserve fertility; D) infertile patients or patients with history of repeated abortions.

due to non fibroid associated endometrial hyperplasia without atypic cells (4).

The perimenopausal patients who do not satisfy the inclusion criteria for the cyclic treatment are submitted to hysterectomy after 3 months of pretreatment with GnRH analogues. In the cases of perimenopausal patients included in the cyclic treatment protocol, after 3 months of therapy, clinical, ultrasound and Doppler flow assessment is repeated.

Response is considered inadequate if the menometrorrhagic and/or pain symptoms persist, if the reduction in myoma volume is smaller than 20%, if the Doppler flow indices are unchanged, and if side effects are relevant; in these cases, hysterectomy is performed. When response is adequate, the GnRH analogue therapy is continued, supplemented by an oestrogen/progestogen combination (Premarin 125 mg \times 25 days + MPA 5 mg from day 16 to day 25) to reduce the extent of bone mineral loss and the GnRH agonist side effects. At regular intervals

(every 6 months) therapy is discontinued to see whether menses resume, and the evaluation of ultrasound, Doppler flow, bone mineral and hormonal parameters is repeated, so as to adjust the steroid dosage and to define when to restart the GnRH analogue treatment, which can be posticipated until symptoms reappear, including increased myoma volume or higher flow indexes. The therapy with GnRH analogues will also be discontinued should a rare (2%) complication occur, that is, genital bleeding due to massive myoma necrosis with hyalinosis; in these cases hysterectomy is promptly performed.

During this trial, started in January 1991, we enrolled 18 patients in the cyclic treatment protocol. In 5 cases therapy was discontinued after the first three months due to inadequate response (4 cases) or to side effects (1 case; vasomotor symptoms, excruciating headache). Of the 13 patients continuing the treatment, only 3 concluded the first cycle and have been off the therapy for a maximum of 3

GnRHa CYCLIC TREATMENT

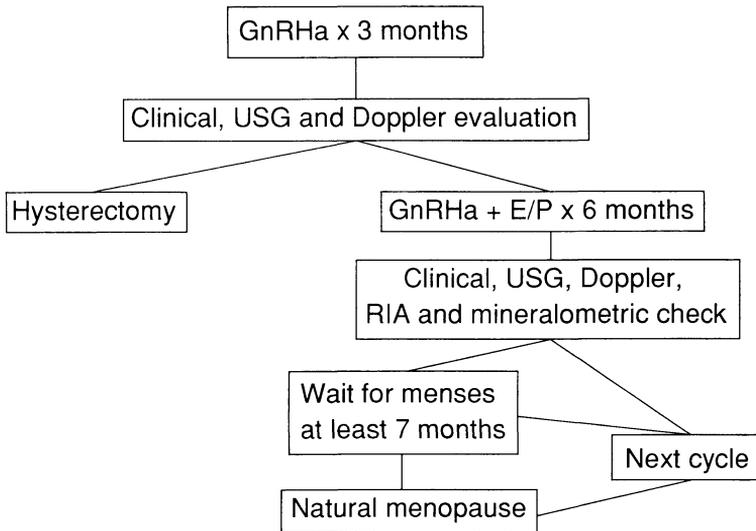


Fig. 2. — Cyclic treatment protocol for perimenopausal patients with fibroids.

months, all of them are still in amenorrhoea. The ultrasound and flow parameters of these three patients do not differ from those observed at 3 months, but we need to wait either for their first menstruation to verify if the disease resumes, or at least 7 months to suppose a transition towards the natural menopause, to be confirmed by RIA (see Fig. 2).

Group B (Young patients, symptomatic or with large myomas, with no wish for more children).

In this group, the initial diagnostic assessment is extremely important in the decision to treat, bearing in mind the limits of GnRH analogue therapy, i.e. myoma regrowth at discontinuation and impossibility to perform very long term treatments because of bone mineral loss. In case of isolated submucous or subserous myomas, a 3-month pretreatment with GnRH analogues should be administered, with monthly controls to prevent

excessive tumour shrinkage, followed by the specific endoscopic surgery. In case of intramural extension of the myomas, mainly subserous, and in all cases in which it exists a clinical indication for laparotomic myomectomy, this should be preceded by a 3 to 6 months pretreatment with a GnRH analogue and the patient should be informed about the risk of postoperative relapse. In case of multiple large size intramural myomas or in case of in toto fibromatous uterus, the patient should be scheduled for hysterectomy after a pretreatment with GnRH analogues, due to the benefits illustrated above.

Group C (Young patients, symptomatic or with large myomas, wishing to preserve fertility).

In these patients radical surgery can be considered only once they have completed their reproductive plans. The initial diagnostic assessment enables us to plan the most appropriate conservative treatment,

which in any case cannot be confined to medical therapy alone.

Also in these patients submucous and subserous lesions will benefit from an adequately prepared endoscopic treatment, as illustrated above. In this group of patients the protocol should consider 2 variables: extent of myomatosis and time to next pregnancy. If the site and size of myomas are such as to interfere with pregnancy or if the woman's wish to preserve her reproductive capacity is not aimed at one single pregnancy planned in the short term, then the approach should envisage a laparotomic myomectomy following a 6 months pretreatment with GnRH analogues to reduce as much as possible intraoperative bleeding, frequently more abundant in this surgical procedure than in hysterectomy. If size and site of myomas are not hazardous for reproduction and the time to next pregnancy is not long (less than 1 year), a watchful wait can be planned for the pregnancy, to postpone the decision about the surgical treatment of myomas after breastfeeding.

In case of intramural or multiple submucous or large myomas, or in toto fibromatous uterus, that is, when myomectomy is likely to end up in hysterectomy, the patient can be recommended to enter an on/off medical treatment protocol (following Blumenfeld) with 3 months of GnRH analogue therapy, 6 months of interruption and 3 more months of treatment followed by adequate USG, Doppler and bone mineral density follow-up to decide whether and when to retreat the patient with GnRH analogue-E/P combination protocols.

Group D (Infertile patients or patients with repeated abortions).

In case of subserous myoma – should the diagnosis be made in the course of laparoscopy – this can be directly remo-

ved during the laparoscopic procedure, and a 3 months postoperative GnRH analogue therapy may be performed.

If the subserous myoma is screened before laparoscopy, we can resort to a 3 month GnRH analogue pretreatment and subsequent monthly ultrasound follow-up to decide the most appropriate moment to perform the operative laparoscopy, to avoid excessive myoma shrinkage that would make it difficult or even impossible to visualize the myoma during the procedure.

In case of intracavitary fibroid, this must be removed due to its inevitable impact on embryo implantation: thus pretreatment with GnRH analogues will be planned, with subsequent tumour ablation by hysteroscopy. In case of intramural myoma, its possible interference with reproduction should be carefully evaluated. Usually fibroids do not negatively interfere with the reproductive potential, though some Authors report endometrial vascularization changes in the myoma area, with decreased possibility of embryo implantation, reduced capacity of the uterus to carry out pregnancy with increased tendency to miscarriage, and possible increase in mother-foetus morbidity. We believe we should intervene with medical or surgical therapy only when sure that the fibromatous lesion will interfere with the reproductive process, as in the case of a small precornual myoma with impaired oviductal function. In such cases we only perform medical treatment with GnRH analogues for 3 months and subsequently we follow the diagnostic-therapeutic procedures for infertility. In case of intramural myoma with severe abnormalities of the cavity, medical therapy will be prescribed for 3 months, followed by hysteroscopic reassessment of the cavity; if it has returned to normal, we resort to assisted fertilization techniques to achieve pre-

gnancy, if the cavity is still deeply altered, myomectomy will be performed.

For large intramural myomas that do not significantly deform the cavity, the need for surgery is evaluated only after completing all the relevant diagnostic and therapeutic procedures including assisted reproduction techniques. In these cases we perform laparotomic myomectomy after a 3 month pretreatment with GnRH analogues. Finally, in cases of sterile perimenopausal patients, the approach differs in the duration of the GnRH analogue therapy, not exceeding 2 months, and in that, immediately after, an assisted reproduction programme is implemented, exploiting the ovarian desensitization if the basal FSH levels of the patient are below 15 mIU/ml.

CONCLUSION

In conclusion, the introduction of GnRH analogues in the treatment of fibroids has had an enormous impact on the disease, making surgery easier and solving its menometrorrhagic complications; moreover, it is a remarkable example of modern and thoughtful integration between a correct use of the new molecules made available by pharmacologic research and the established principles of surgical therapy, which remains a cornerstone in the cure of this disease.

REFERENCES

- 1) Robbins S. L., Copram R. S.: "Leiomyomata (fibromyoma), in the pathogenic basis of disease". Philadelphia, WB Saunders, pp. 1271, 1979.
- 2) National Center for Health Statistic: "Hysterectomies in the USA, 1965-1984. Vital and Health Statistic". Series 13, No. 92, Publ. No. (PHS) 88-1753, Public Health Service, Washington, DC, Government Printing Office, 1987.
- 3) Filicori M., Hall D. A., Loughlin J. S., Rivier J., Vale W., Crowley W. F. Jr.: "A conservative approach to the management of uterine leiomyoma: pituitary desensitization by a luteinizing hormone-releasing hormone analogue". *Am. J. Obst. Gyn.*, 1983, 65, 389.
- 4) Colacurci N., De Placido G., Galasso M., Mollo A., Perino A., Cittadini E.: "The use of GnRH agonists depot for the treatment of dysfunctional uterine bleeding". *Acta Europaea Fertilitatis*, 1991, 22, 4.
- 5) Lumsden M. A., West C. P., Baird D. T.: "Goserelin therapy before surgery for uterine fibroids". *Lancet*, 1987, 1, 36.
- 6) Friedman A. J., Barbieri R. L., Doubilet P. M., Fine C., Schiff I.: "A randomized, double-blind trial of gonadotropin-releasing hormone agonist (leuprolide) with or without medroxy-progesterone acetate in the treatment of leiomyomata uterine". *Fertil. Steril.*, 1988, 49, 404.
- 7) Friedman A. J.: "Vaginal hemorrhage associated with degenerating submucous leiomyomata during leuprolide acetate treatment". *Fertil. Steril.*, 1989, 52, 152.

Address reprint requests to:

U. MONTEMAGNO
Dept. OB/GYN
Medical School - University
Federico II, Naples
Via Pansini, 5 - 80131 Naples (Italy)