

# Role of goserelin-depot in the clinical management of uterine fibroids

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**Summary:** On 30 women suffering from uterine fibroids, the monthly subcutaneous administration of goserelin depot (3.6 mg) for 6 (n=22) or 12 months (n=8) induced an about 50% shrinkage of uterus and fibroid volume, and within 3 months, an increase in the haematocrit value, with no metabolic side effects or detectable bone demineralization, evaluated by single photon absorptiometry at distal radius. Both uterine and fibroid volumes reversed to pretreatment values after 3 months of goserelin depot withdrawal. In comparison with untreated subjects, on another 10 patients a three month administration of goserelin depot reduced the loss of blood during the surgical removal of the uterus or fibroids. Present data indicate that goserelin depot is effective and relatively safe in the medical management of uterine fibroids. Although, goserelin depot cannot yet be proposed as a definite medical therapy, it may represent a useful instrument in the presurgical management of uterine fibroids.

## INTRODUCTION

Uterine fibroids, the common pelvic tumors that occur in up to 20% women over 30 years of age, are the most frequent cause of gynecological surgery<sup>(1)</sup>. Estrogen and progesterone receptors are present in fibroid tissue<sup>(2, 3)</sup>, with estrogen probably exerting a stimulus and progesterone an inhibition of fibroid growth<sup>(4, 5)</sup>. The administration of progesterone and progestins has, however provided inconsistent clinical results<sup>(4, 6-8)</sup>, and its therapeutical role has recently been chal-

lenged<sup>(9-11)</sup>. With the advent of gonadotropin-releasing hormone agonists, particularly the long acting compounds, medical ovariectomy has represented a new approach to the clinical medical management of uterine fibroids<sup>(12-15)</sup>.

In this study we investigated the advantages and disadvantages of using a long-term GnRH-agonist, goserelin depot (Zoladex, ICI), as medical treatment or pre-surgical management of uterine fibroids.

## MATERIALS AND METHODS

The study was performed on 50 subjects, 30 to 49 years of age, in good health, with ultrasound evidence of uterine fibromatosis and fibroids. Every 28 days, starting on the follicular phase of the menstrual cycle (days 5-7), a subcutaneous injection of 3.6 mg of goserelin depot, was administered for 6 months to 22 subjects, and for 12 months to 8 subjects. The other 20

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subjects, who needed surgical removal of fibroids or uterus, were randomly allocated for 3 months to no treatment or goserelin depot administration.

Ultrasound evaluation of uterus and main fibroid volumes, as well as bone mineral density (BMD) at the distal radius, by single photon absorptiometry, were performed beforehand, at monthly intervals during treatment, and 3 months after goserelin depot cessation. Plasma levels of LH, FSH, E2, total cholesterol, HDL-cholesterol, HDL2-cholesterol, HDL3-cholesterol, triglycerides, glucose and haematocrit values were analyzed during goserelin depot treatment. In the group treated for 3 months prior to surgery, the amount of blood loss, as aspirated blood, at surgery, was compared with that of controls, and considered as an indirect index of uterus vascularity and surgical difficulty.

## RESULTS

In all subjects maximal inhibition of LH, FSH and E2 secretion was achieved after only 28 days of goserelin depot administration. Within 1 month, LH levels decreased below the assay sensitivity (1.5 IU/L), FSH levels to about 3.5 IU/L and E2 to postmenopausal values of about 20 pg/ml. From a clinical point of view, these endocrine modifications were associated with amenorrhea, which occurred in 100% of subjects within the second cycle of goserelin depot administration. In all subjects amenorrhea had disappeared at the third month of goserelin withdrawal.

On the 22 subjects treated for 6 months, a 50% shrinkage of both uterus volume ( $90 \pm 10$  vs  $180 \pm 10$  cm<sup>3</sup>;  $p < 0.05$ ) and main fibroids ( $15 \pm 2$  vs.  $33 \pm 10$  cm<sup>3</sup>;  $p < 0.05$ ), was observed at the end of treatment. An increase of both uterus volume ( $120 \pm 10$  cm<sup>3</sup>) and main fibroids ( $22 \pm 6$  cm<sup>3</sup>) was, however, observed 3 months after goserelin withdrawal.

On the 8 subjects undergoing the 12 month treatment, both uterus ( $310 \pm 30$  cm<sup>3</sup>) and main fibroid volumes ( $48 \pm 12$  cm<sup>3</sup>) were greater ( $p < 0.05$ ) than in the other group of 22 subjects. Maximum shrinkage (about 50%) was achieved after

12 months for the uterus ( $130 \pm 20$  cm<sup>3</sup>;  $p < 0.05$ ) and after 6 months for main fibroids ( $23 \pm 3$  cm<sup>3</sup>;  $p < 0.05$ ). Three months after goserelin depot withdrawal, both uterus ( $180 \pm 15$  cm<sup>3</sup>) and main fibroid volumes ( $35 \pm 7$  cm<sup>3</sup>) were increased, but uterus volume was still lower ( $p < 0.05$ ) than beforehand.

In all subjects, no modification in plasma lipid and glucose levels was observed. From pretreatment values, haematocrit reached maximal values within 3 months of goserelin depot administration, both in subjects treated for 6 ( $31 \pm 3\%$  vs  $40 \pm 2\%$ ;  $p < 0.01$ ) or 12 months ( $28 \pm 2\%$  vs.  $39 \pm 2\%$ ;  $p < 0.01$ ). Thereafter, in both groups, haematocrit remained at this maximal levels. BMD did not significantly decrease during goserelin depot treatment, either in the group treated for 6 ( $415 \pm 30$  vs  $420 \pm 17$  mg/cm<sup>2</sup>) or 12 ( $412 \pm 28$  vs  $425 \pm 30$  mg/cm<sup>2</sup>) months.

## DISCUSSION

Present data confirm the clinical usefulness of goserelin depot in shrinking uterine fibroids. Although, the reduction of about 50% in uterus volume may be consequent to an effect on normal myometrial cells, the clinical efficacy on fibroid cells is confirmed by the comparable reduction of individually measurable fibroids. The effect of goserelin depot, probably exerted with various mechanisms<sup>(16-18)</sup>, was relevant and not associated to major metabolic side effects or marked increases in bone demineralization. Furthermore, consequent to the induced amenorrhea, haematocrit, previously below the normal range, increased within 3 months to normal levels with no need of additional therapies.

Although the beneficial effect of goserelin depot was almost completely reversed after drug withdrawal, the increase in haematocrit associated with a reduced blood loss during the surgical removal of uterine fibroids or uteri, renders gosere-

lin depot a useful approach to the surgical management of uterine fibroids<sup>(15)</sup>. In several subjects, close to the menopause, goserelin depot may represent a useful definitive treatment for uterine fibroids, by inducing an earlier medical menopause. By contrast, in young subjects, the impossibility of maintaining a prolonged menopause and the reversibility of goserelin depot effects represent strong limitations to its indication as a definitive medical treatment for uterine fibroids. The possibility of administering goserelin depot in association with therapies aimed at reducing the consequences of hypoestrogenism may, however, amplify the therapeutical use of this GnRH analog, and for this reason it requires careful and focused investigation.

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