FERTILITY AND STERILITY®
VOL. 75, NO. 3, MARCH 2001

Published by Elsevier Science Inc.
Printed on acid-free paper in U.S.A.

Administration of somatostatin analogue reduces uterine and myoma volume in women with uterine leiomyomata

Uterine leiomyomata are the most common benign tumors in women, occurring in 20%–25% of women during their reproductive years. The etiology of myomas has not been fully elucidated. Growth of leiomyomas is promoted by various factors. Hypoestrogenism, which occurs after the postmenopause and during therapy with gonadotropin-releasing hormone (GnRH) agonist, reduces the size of leiomyomas; this observation indicates that the tumor is estrogen dependent (1). Similarly, marked regression of leiomyomas after therapy with the potent antiprogestin RU486 indicates a probable stimulatory effect of progesterone on the tumor (2). Increasing evidence shows that growth factors may play a role in the generation or growth of this tumor.

Forty years ago, Grattarola and Li (3) demonstrated that growth hormone was synergistic with estradiol in causing an increase in uterine weight in hypophysectomized and ovariectomized rats. More recently, the presence of growth hormone receptor messenger RNA was demonstrated in the normal myometrium and myomas, suggesting a possible role of growth hormone in the development of myoma (4). Of note, it has been shown that acromegaly, a disorder characterized by high levels of growth hormone, is associated with a high incidence of uterine leiomyoma (5).

Insulin-like growth factor I (IGF-I) and its receptor have been identified in myometrium and leiomyomas (6–9), and some studies have shown increased IGF-1 expression in leiomyoma compared with the adjacent myometrium (10–12). Thus, growth hormone may exert a direct effect on the uterus by interacting with growth hormone receptor and an indirect effect by increasing hepatic synthesis and secretion of IGF-1.

Lanreotide is a long-acting somatostatin analogue that has been shown to reduce spontaneous growth hormone secretion in healthy men (13). We evaluated the effect of administration of a lanreotide depot formulation, 30 mg, in seven women with uterine myomas presenting to the Unit of Gynecological Endocrinology, Department of Obstetrics and Gynecology, Siena University, Siena, Italy.

All women were healthy and of reproductive age (mean age [±SD] 37 ± 5 years). Exclusion criteria were hepatic, renal and endocrinologic dysfunction, and use of sex steroids or GnRH analogues less than 1 year before the start of the study. The women were informed of the aim of the study and its experimental nature and gave written consent.

Two of the authors performed baseline ultrasonography when a transvaginal probe was performed to evaluate the uterus and ovaries. The intra- and interobserver coefficients of variations in measurement of ultrasonographic volume of uterus and myoma were 6% and 8%, respectively.

Uterine and myoma volume were calculated by using the formula $V = 4/3\pi \times R1 \times R2 \times R3$, where R=50% of the transvaginally assessed diameter of uterus or the fibroid in one dimension (14).

Lanreotide, 30 mg, in a depot formulation was administered on the second day of the cycle and every 14 days for 3 months. Ultrasonography was performed and blood tests were obtained for hormonal evaluation before therapy, after therapy, and 3 months after the end of therapy, during the follicular phase of the menstrual cycle.

The study was approved by the institutional review board of the University of Siena. Uterine and myoma volumes and hormone levels were compared by using analysis of variance. $P<.05$ was considered significant.

Estradiol (90 ± 34 pg/mL) and follicle-stimulating hormone (7 ± 2 mIU/mL) plasma levels demonstrated the fertile status of the studied women. Mean basal uterine volume was 305 ± 31 cm^3. Ultrasonography showed a 24% ± 6.8% reduction in uterine volume after 3 months of therapy ($P<.05$). A significant reduction of about 17% ± 4.1% was observed 3 months after the end of treatment ($P<.05$) (Fig. 1). Mean basal myoma volume was 24 ± 6 cm^3. Mean myoma volume was reduced by 41.6% ± 11% ($P<.05$) after therapy and 29.2% ± 7% ($P<0.5$) 3 months after the end of treatment. Hormone assays showed unchanged levels of follicle-stimulating hormone and estradiol during therapy, but plasma concentrations of growth hormone and IGF-I were decreased (baseline values, 3.4 ± 0.8 ng/mL and 2.9 ± 0.6 IU/mL, respectively; values after 3 months of therapy, 0.7 ± 0.3 ng/mL and 0.6 ± 0.2 IU/mL; $P<.05$).

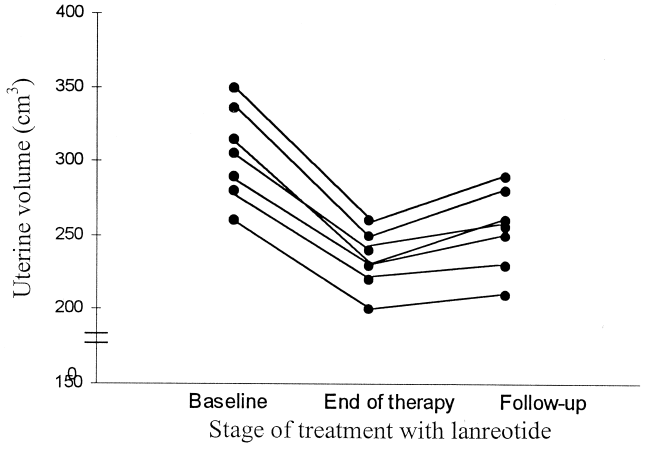
Received July 19, 2000; revised and accepted September 12, 2000.

Reprint requests: Vincenzo De Leo, M.D., Department of Obstetrics and Gynecology, University of Siena, Policlinico Le Scotte, 53100 Siena, Italy (FAX: 39-0577-233464; E-mail: deleo@unisi.it).

0015-0282/01/$20.00
PII S0015-0282(00)01738-6

FIGURE 1

Reduction in uterine volume after lanreotide treatment.



De Leo. Uterine leiomyomata and somatostatin. Fertil Steril 2001.

Administration of the somatostatin analogue lanreotide resulted in a reduction in uterine and myoma volume in seven fertile women. The mean reduction was about 24% for total uterus dimension and 41.6% for myoma volume. This finding unequivocally demonstrates the effect of growth hormone on myomas and that growth hormone is involved in the pathogenesis of uterine fibromyomas.

It was recently shown that women with acromegaly, a disorder characterized by high plasma concentrations of growth hormone, have an 81% prevalence of leiomyoma (5). Growth hormone receptor messenger RNA has been identified in human normal myometrium and leiomyomas (4). Of note, the amount of growth hormone receptor was similar in all sections regardless of whether women had received pretreatment with GnRH agonist; this finding indicates that estradiol has no role in expression of growth hormone messenger RNA. Growth hormone may have a direct effect on the development of leiomyomas in women, or the effect may be indirect, through IGF secretion.

Recent studies indicate that IGF-I and IGF-II messenger RNA is present in uterine tissue; estrogens have been found to increase levels of this messenger RNA (10, 11, 15, 16). Both IGF-I and IGF-II are expressed in myometrium and leiomyomas, and explants of myomas and myometrium have been shown to secrete IGF-I (6). Leiomyomas are reported to contain more binding sites for IGF-I (but not IGF-II) than normal myometrium (8). This evidence suggests that IGF-I may induce cell proliferation in uterine myomas and play a role in the formation and growth of myomas.

In conclusion, our study provides important evidence that the growth hormone–IGF system plays a pathogenic role in maintaining uterine fibromyomas and that somatostatin analogue may be an effective new therapy for this condition.

Vincenzo De Leo, M.D.
Antonio la Marca, M.D.
Giuseppe Morgante, M.D.
Filiberto Maria Severi, M.D.
Felice Petraglia, M.D.
Department of Obstetrics and Gynecology, University of Siena, Siena, Italy

References

1. Friedman AJ, Barbieri RL, Doubilet PM, Fine C, Schiff I. A randomized, double-blind trial of a gonadotropin releasing-hormone agonist (leuprolide) with or without medroxyprogesterone acetate in the treatment of leiomyomata uteri. Fertil Steril 1988;49:404–9.
2. Murphy AA, Kettel LM, Morales AJ, Roberts VJ, Yen SSC. Regression of uterine leiomyomata in response to the antiprogestine RU 486. J Clin Endocrinol Metab 1993;76:513–7.
3. Grattarola R, Li CH. Effect of growth hormone and its combination with estradiol-17β on the uterus of hypophysectomized-ovariectomized rats. Endocrinology 1959;65:802–10.
4. Sharara FI, Nieman LK. Growth hormone receptor messenger ribonucleic acid expression in leiomyoma and surrounding myometrium. Am J Obstet Gynecol 1995;173:814–9.
5. Choen O, Schindel B, Homburg R. Uterine leiomyomata—a feature of acromegaly. Hum Reprod 1998;13:1945–6.
6. Rein MS, Friedman AJ, Pandian MR, Heffner LJ. The secretion of insulin-like growth factor-I and II by explant cultures of fibroids and myometrium from women treated with a gonadotropin-releasing hormone agonist. Obstet Gynecol 1990;76:388–94.
7. Giudice LC, Irwin JC, Dsupin BA, Pannier EM, Jin IH, Vu TH, et al. Insulin-like growth factor (IGF), IGF binding protein (IGFBP), and IGF receptor gene expression and IGFBP synthesis in human uterine leiomyomata. Hum Reprod 1993;8:1796–806.
8. Chandrasekhar Y, Heiner J, Osuampke C. Insulin-like growth factor I and II binding in human myometrium and leiomyomas. Am J Obstet Gynecol 1992;166:64–9.
9. Tommola P, Pekonen F, Rutanen E. Binding of epidermal growth factor and insulin-like growth factor I in human myometrium and leiomyoma. Obstet Gynecol 1990;74:658–62.
10. Hoppener JWM, Mosselman S, Roholl PJM. Expression of insulin-like growth factor I and II genes in human smooth muscle tumours. EMBO J 1988;7:1379–85.
11. Boehm KD, Daimon M, Gorodeski I, Sheean LA, Urian WH, Ilan J. Expression of the insulin-like and platelet-derived growth factor genes in human uterine tissues. Mol Reprod Dev 1990;27:93–101.
12. Gloudemans T, Prinsen I, Van Unnik JAM, Lips CJ, Den Otter W, Sussenbach JS. Insulin-like growth factor gene expression in human smooth muscle tumors. Cancer Res 1990;50:6689–95.
13. Kuhn JM, Basin C, Mollard M, de Rouge B, Baudoin C, Obach R, et al. Pharmacokinetic study and effects on growth hormone secretion in healthy volunteers of the new somatostatin analogue BIM 23014. Eur J Clin Pharmacol 1993;45:73–7.
14. Friedman AJ, Barbieri RL, Benacerraf BR, Schiff I. Treatment of leiomyomata with intranasal or subcutaneous leuprolide, a gonadotropin-releasing hormone agonist. Fertil Steril 1987;48:560–4.
15. Norstedt G, Levionvitz A, Ericksson H. Regulation of uterine insulin-like growth factor I mRNA and insulin-like growth factor II mRNA by estrogen in the rat. Acta Endocrinol (Copenh) 1989;120:466–72.
16. Murphy LJ, Murphy LC, Frisen HG. A role for the insulin-like growth factors as estromedins in the rat uterus. Trans Assoc Am Physicians 1988;99:204–14.