Case Report

Received: November 6, 1996

Accepted: November 18, 1996

Gynecol Obstet Invest 1997;43:276-277

Reduction in the Size of a Uterine Leiomyoma following Discontinuation of an Estrogen-Progestin Contraceptive

R.L.	Robert L.	Barbieri
------	-----------	----------

Department of Obstetrics, Gynecology and Reproductive Biology, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass., USA

Key Words

Uterine leiomyomata

Oral contraceptives

Size reduction, uterine leiomyoma

Abstract

The effects of estrogen-progestin oral contraceptives on the volume of uterine leiomyomata is not well characterized. In this case report, a 45-year-old woman with a symptomatic uterine leiomyoma was observed to have a 47% reduction in myoma volume after discontinuation of an oral contraceptive. The volume of uterine leiomyomata may be influenced by oral contraceptives.

Robert L. Barbieri, MD, Department of Obstetrics, Gynecology and Reproductive Biology, ASB1-3, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115 (USA), Tel. +1 617 732 4265, Fax +1 617 277 1440, E-Mail rlbarbieri@bics.bwh.harvard.edu

Introduction

Uterine leiomyomata are the most common pelvic tumors of women. The etiology of uterine leiomyomata is not completely characterized, but it appears that these tumors arise after a somatic mutation in a progenitor cell [1]. Uterine leiomyomata are monoclonal [2], and many are cytogenetically abnormal [3]. Genes in the high mobility group family, including HMGI-C [4], are mutated in some leiomyomata.

Estrogen and progestins influence the volume of uterine leiomyomata. Administration of the gonadotropin-releasing hormone (GnRH) agonist leuprolide acetate suppresses circulating estradiol and progesterone and is associated with an approximately 45% reduction in mean uterine volume in women with leiomyomata [5]. In women with leiomyomata being treated with a GnRH agonist, the simultaneous administration of estrogen or progestin can block the decrease in leiomyomata and uterine volume that would be expected with GnRH agonist treatment [6, 7]. The effects of estrogen-progestin oral contraceptives on the uterine leiomyomata volume are not well studied.

Case Report

A 45-year-old woman presented with right lower quadrant pain. The patient received regular gynecologic care and had no chronic medical problems. She had taken a combination estrogen-progestin contraceptive containing 0.35 µg of ethinyl estradiol and 0.35 mg of norgestrel for more than 5 years. She had regular menses, of normal flow and duration. She did not smoke cigarettes. The pain developed over a few days and was crampy. She had no uterine bleeding. Examination of the abdomen demonstrated no masses and no peritoneal signs. Pelvic examination revealed a normal vulva and vagina. The cervix was normal. The uterus was enlarged to a size corresponding to 12-14 gestational weeks, with a mass at the right fundal

margin of the uterus. No separate adnexal masses were palpable. Pelvic ultra-sonography demonstrated normal adnexa and multiple leiomyomata with a large dominant leiomyoma measuring $7.2 \times 5.8 \times 5.5$ cm at the uterine fundus. In the posterior portion of the uterus, another leiomyoma 1 cm in diameter was noted. The oral contraceptive was discontinued. The patient's pain resolved, and normal menses continued. Follow-up pelvic examination 4 months after discontinuing the oral contraceptive demonstrated a uterus of a size of 8-10 gestational weeks. Repeat pelvic sonography, performed approximately 4 months after discontinuing the oral contraceptive, demonstrated a single serosal leiomyoma measuring $5.9 \times 4.6 \times 4.4$ cm. The leiomyoma volume was calculated using a formula for an ellipsoid ($\frac{4}{3} \times 3.14 \times R1 \times R2 \times R3$), where R is the radius. The leiomyoma volume decreased by 47% after discontinuation of the oral contraceptive (from 120 to 63 cm³). Follow-up pelvic sonography, 12 months after discontinuing the oral contraceptive, demonstrated no further change in myoma volume ($5.4 \times 5.3 \times 4.2$ cm; 63 cm³). Menses remained regular, with normal duration and flow.

KARGER

E-Mail karger@karger.ch Fax+ 41 61 306 12 34 [http:// www. karger. ch](http://www.karger.ch)

© 1997 S. KargerAG, Basel 0378-7346/97/0434-0276\$ 12.00/0

Discussion

The size of uterine leiomyomata is influenced by estradiol and progesterone. In a hypoestrogenic state (menopause or treatment with a GnRH agonist), the administration of estrogens and progestins can cause an increase in uterine volume in women with leiomyomata. Sener et al. [8] randomized menopausal women with small asymptomatic uterine leiomyomata to receive 1 of 2 hormone replacement regimens. The women who were randomized to receive transdermal estradiol (50 µg) and medroxyprogesterone acetate (5 mg daily) had a 38% increase in the diameter of their largest myoma. Two of the 20 women on this dose of hormone replacement had exceptionally large increases (300 and 400%) in the diameter of the leiomyoma. This suggests that a minority of menopausal women are especially sensitive to the effects of exogenous estrogens and progestins on leiomyoma volume. A second group of women were randomized to receive conjugated equine estrogen (0.625 mg daily) and medroxyprogesterone acetate (2.5 mg daily). This hormone replacement regimen caused no change in the diameter of the largest leiomyoma. One explanation for this finding is that in a hypoestrogenic state, there is a relationship between the dose of exogenous estrogens and/or progestins and the magnitude of the change in leiomyomata diameter.

Carr et al. [7] randomized women with uterine leiomyomata to receive either leuprolide acetate depot (3.75 mg i.m. every 4 weeks) plus a placebo pill or leuprolide acetate depot plus medroxyprogesterone acetate (20 mg daily). The women who received the leuprolide acetate plus a placebo pill had a 26% reduction in uterine volume after 12 weeks of treatment. The women who received the leuprolide acetate plus medroxyprogesterone acetate had no change in the uterine volume after 12 weeks of treatment. This suggests that the progestin, medroxyprogesterone acetate, blocks the effect of a hypoestrogenic state on uterine volume in women with leiomyomata.

The effects of estrogens and progestins on leiomyoma volume in premenopausal women is not well studied. A small number of case reports suggests that in an occasional woman with leiomyomata, treatment with estrogen-progestin oral contraceptives can be associated with an increase in uterine volume [9, 10]. However, given the small number of such cases which have

been reported, and the high prevalence of leiomyomata and oral contraceptive use, it is probable that only a minority of women with leiomyomata are likely to experience a change in uterine volume with oral contraceptive use. Randomized studies will be needed to definitively address this issue.

The case presented in this report is an example of a large change in uterine leiomyoma volume associated with the discontinuation of an oral contraceptive. In women on oral contraceptives, with clinically significant uterine leiomyomata, clinicians might consider the discontinuation of the oral contraceptive as low-risk intervention that might be associated with a decrease in uterine volume.

References

- Barbieri RL, Andersen J: Uterine leiomyomata: The somatic mutation theory. *Semin Re-prod Endocrinol* 1992;10:301-309.
- Townsend DE, Sparkes RS, Baluda MC, McClelland G: Unicellular histogenesis of uterine leiomyomas as determined by electrophoresis of glucose-9-phosphate dehydrogenase. *Am J Obstet Gynecol* 1970;107:1168-1173.
- Rein MS, Friedman AJ, Barbieri RL, Pavelka K, Fletcher JA, Morton CC: Cytogenetic abnormalities in uterine leiomyomata. *Obstet Gynecol* 1991;77:923-926.
- Schoenmakers EF, Wanschura S, Mols R, Bul-lerdiek J, Van der Berghett, Van der Ven WJ: Recurrent rearrangements in the high mobility group protein gene, HMGI-C, in benign mesenchymal tumors. *Nat Genet* 1995;10:436-441.
- Friedman AJ, Harrison-Atlas D, Barbieri RL, Benaceraff B, Gleason R, Schiff I: A randomized, placebo-controlled, double-blind study evaluating the efficacy of leuprolide acetate depot in the treatment of uterine leiomyomata. *Fertil Steril* 1989;51:251-256.
- 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;49:404-409.
- Carr BR, Marshburn PB, Weatherall PT, Bradshaw KD, Breslau NA, Byrd W, et al: An evaluation of the effect of gonadotropin-releasing hormone analogs on uterine leiomyomata volume by magnetic resonance imaging: A prospective, randomized, double-blind, placebo-controlled crossover trial. *J Clin Endocrinol Metab* 1993;76:1217-1223.
- Sener AB, Seckin NC, Ozmen S, Gokmen O, Dogu N, Ekici E: The effects of hormone replacement therapy on uterine fibroids in postmenopausal women. *Fertil Steril* 1996;65: 354-357.
- West BC Jr: Effects of certain contraceptive pills on uterine myomas. *NC Med J* 1970;31: 14-16.
- John AH, Martin R: Growth of leiomyomata with estrogen-progestogen therapy. *J Reprod Med* 1971;6:56-58.

Uterine Myomata and Contraceptives

Gynecol Obstet Invest 1997;43:276-277