Administration of goserelin acetate after uterine artery embolization does not change the reduction rate and volume of uterine myomas

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Objective: To determine if goserelin immediately after uterine artery embolization (UAE) affected myoma reduction.
Design: Randomized pilot study (level 1).
Setting: Teaching hospital.
Patient(s): Twenty-six women.
Intervention(s): All patients underwent UAE, and then 12 patients received 10.8 mg of goserelin 24 hours later. The treatment group was 5 years older: 43 versus 37.7 years. Uterine and myoma volumes were measured by ultrasound 2 weeks before UAE and at 3, 6, and 12 months.
Main Outcome Measure(s): Uterine and fibroid volumes.
Result(s): Pretreatment uterine volume was 477 versus 556 cm^3, and dominant fibroid volume was 257 versus 225 cm^3 in the control versus goserelin groups. Analysis of variance measurements indicated that the change over time did not significantly differ between the two groups. By 12 months, the control group had a mean uterine volume reduction of 58%, while the goserelin group had a reduction of 45%. Dominant fibroid changes over time did not differ between the two groups. At 12 months, the mean fibroid volume had decreased by 86% and 58% in the control and goserelin groups, respectively.
Conclusion(s): The addition of goserelin therapy to UAE did not alter the reduction rate or volume of uterine myomas. (Fertil Steril® 2006;85:1478–83. ©2006 by American Society for Reproductive Medicine.)

Key Words: Goserelin, uterine artery embolization, uterine fibroids, myomas, leiomyomas

Uterine fibroids (myomas) are the most common pelvic tumors, occurring in 25%–40% of premenopausal women (1, 2). A survey of a random sample of 1,364 women aged 35–49 in an urban United States health plan with approximately 50% black membership demonstrated by transabdominal and transvaginal ultrasound a cumulative incidence of fibroids of >80% for blacks and nearly 70% for whites. Fibroid incidence rates were significantly higher for blacks at all ages (3). As a rule, fibroids may cause no symptoms and require no treatment. However, 20%–50% of women with myomas will experience tumor-related symptoms. Depending on location, and unrelated to uterine size, they can cause heavy, irregular, and prolonged menstrual bleeding leading to iron deficiency anemia and reproductive dysfunction (4). In addition, they may cause pelvic discomfort, bloating, and bowel and bladder dysfunction from pressure exerted by the volume (bulk symptoms) and they account for up to 35% of all hysterectomies (5). Fibroids appear after menarche, proliferate and grow during the reproductive years, stabilize and/or regress after natural or induced menopause (2, 6), and may regrow after hormone therapy (7). Histologically, they arise from a single muscle cell, and they grow under the influence of sex hormones, including estrogen and P (6, 8–12), their effects being modulated by local growth factors (8, 11, 12).

Treatment options are usually tailored to take into account the patient's symptoms, age, and needs as well as the experience of the therapist and the availability of therapy. Therapies include watchful waiting, myomectomy, myolysis, and finally hysterectomy (13).

Since the introduction of uterine artery embolization (UAE) to treat fibroids before hysterectomy in 1995 by Ravina in France (14), selective uterine artery occlusion has been shown to be a global, safe, effective, and durable treatment of symptomatic fibroids in women for whom medical and surgical treatments are ineffective, contraindicated, or refused (15–22). The mechanism of action has been postulated to be transient uterine ischemia, whereby the uterus recovers and survives and the fibroids undergo hyaline degeneration and necrosis (19). It has been found that UAE significantly reduces menorrhagia, dysmenorrhea, and fibroid bulk–related effects in approximately 90% of women treated and reduces by approximately 50% the myoma volume within 6 months of treatment (15–22).

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In addition to and/or in conjunction with surgical treatment, the current approach in the management of uterine fibroids includes a variety of medical therapies consisting of manipulation of steroid hormone levels and their receptors. For example, danazol alone (23), danazol after GnRH agonists (GnRH-a) (24), mifepristone (RU486) with or without GnRH-a (25–28), and intermittent GnRH-a (29) have been used to treat uterine myomas. Raloxifene has also been shown to shrink uterine leiomyomas after menopause (30).

Gonadotropin-releasing hormone agonists inhibit steroidogenesis via pituitary down-regulation and induce a transient menopausal state. The profound hypoestrogenism secondary to GnRH-a treatment leads to fibroid shrinkage on average of 50% by the third month of therapy (31). However, after cessation of GnRH-a therapy the fibroid volume rebounds to pretreatment levels as early as 3 months and continues to grow (2, 19, 31–33).

When used separately, UAE and GnRH-a treatments each reduce fibroid size by approximately 50%. We hypothesized that both therapies given together might act synergistically and alter the reduction rate and volume of symptomatic uterine myomas. This pilot study was designed to test the above hypothesis by randomly treating women with symptomatic fibroids with UAE alone and with a GnRH-a given approximately 24 hours after UAE.

MATERIALS AND METHODS

Institutional Review Board approval was obtained to treat up to 30 women with symptomatic uterine fibroids in this pilot study. After informed consent and inclusion and exclusion criteria, 26 women received UAE. These women were randomized before treatment by computer-generated random numbers and sealed envelopes into receiving UAE alone or UAE plus goserelin acetate depot (Zoladex 10.8 mg, AstraZeneca, Mississauga, ON, Canada) given SC approximately 24 hours after UAE by the senior author (GAV). Eligible subjects included women referred to one gynecologist (GAV) with fibroid-related symptoms such as dysmenorrhea and abnormal uterine bleeding or bulk-related symptoms such as bowel or bladder dysfunction and pelvic pressure and/or pain. Uterine fibroid size and patient age were not causes for exclusion in the study. Women with active pelvic inflammatory disease or renal insufficiency (serum creatinine >150 μmol/L) and those desirous of fertility were excluded.

All women had a detailed history, complete physical and pelvic examination and negative Papanicolaou smears (within 12 months), and endometrial biopsy (within 6 months). Preprocedural investigations included blood screens for prothrombin, partial prothrombin, platelets, hemoglobin, FSH, and creatinine. Transvaginal ultrasound was performed just before UAE (within 2 weeks) and at 3, 6, and 12 months after UAE at the same hospital. All procedures were performed at St. Joseph's Health Care by interventional radiologists skilled in selective angiography and embolization. Selective catheterization of both uterine arteries was completed from a single femoral artery approach. The primary embolic material used was polyvinyl alcohol particles (PVA) of 300–500 μm followed by either gel foam pledgets or coils to occlude the uterine arteries. Routine prophylactic antibiotics were not used.

All patients were admitted to the hospital for at least one overnight stay. The mean hospital stay was 30 hours. Postprocedure pain, manifested by variable degrees of uterine cramping, was controlled by a morphine-based patient-controlled anesthetic pump with the addition of nonsteroidal anti-inflammatory drugs and antipyretics with codeine as required. Patients were discharged when they were able to void, were ambulating with no difficulties, and were tolerating oral pain medication.

Patient follow-up included telephone interviews at 24 hours and at 2 weeks followed by transvaginal ultrasounds and pelvic examination at 3, 6, and 12 months. Ultrasound measurements included maximum diameters in three planes (longitudinal-D_1, anterior-posterior-D_2, and transverse-D_3) of the uterus and the dominant (largest) fibroid. Uterine and fibroid volumes were approximated by the formula (Volume $= \pi/6 \times D_1 \times D_2 \times D_3$) for an ellipsoid shape (19). Transvaginal ultrasound was performed and read by different technicians and radiologists. However, all were blinded to the treatment received by the patients.

Statistical analysis was carried out by the department of biostatistics at the University of Western Ontario.

RESULTS

The baseline descriptive statistics of the two groups are shown in Table 1. Although patients were assigned to each group by randomization, the two groups were not comparable by age. Women in the treatment group averaged 43 years, and in the control group, 37.7 years ($P=.02$). Consequently, in all analyses, age is a potentially confounding variable and the repeated measures analysis of variance age and volume are used as covariates. Age, weight, initial uterine volume, initial fibroid volume, FSH level, hemoglobin concentration, and creatinine concentration were all comparable between the treatment and control groups.

The comparison of dominant fibroid volume over time is shown in Table 2 and Figure 1. A repeated measures analysis of variance of fibroid volume measurements using baseline fibroid volume and age as covariates yielded a nonsignificant P-value for the time versus treatment effect, that is, the change over time did not significantly differ between the two groups ($P=.6263$). At month 12, the fibroid volume in the GnRH-a group had decreased by 58% relative to baseline, while the mean fibroid volume in the control group had decreased by 86% (NS).

The comparisons of uterine volume over time are listed in Table 3 and depicted in Figure 2. The two curves in Figure 2