

Ultrasonographic Prediction of the Efficacy of GnRH Agonist Therapy before Laparoscopic Myomectomy

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Abstract

Study Objective. To assess ultrasonographic prediction of the efficacy of administration of a gonadotropin-releasing hormone (GnRH) analog before laparoscopic myomectomy.

Design. Prospective, randomized study of women treated consecutively from September 1994 to July 1996 (Canadian Task Force classification I).

Setting. Endogyn Service, Private Endoscopic Associates, Naples, and Department of Gynecologic and Pediatric Sciences, Reggio Calabria University, Catanzaro, Italy.

Patients. Sixty-seven infertile women with symptomatic uterine myomata, mainly intramural, undergoing laparoscopic myomectomy.

Interventions. Patients were prospectively randomized in two groups. Group A received preoperative administration of two injections of a depot formulation of leuprolide acetate 28 days apart, and group B underwent direct surgery. In each group we studied the number, diameter, and echogenicity of larger fibroids; resistance index of uterine arteries and myoma vessels; operating time; and blood loss.

Measurements and Main Results. The two groups did not significantly differ in baseline ultrasonographic parameters. Both blood loss ($p < 0.01$) and operating time ($p < 0.05$) were significantly lower in group A. However, operating time was significantly longer when the main myoma was markedly hypoechoic.

Conclusion. Our data confirm the therapeutic efficacy of administration of a GnRH analog before laparoscopic myomectomy in reducing blood loss and decreasing operating time in all cases except those with markedly hypoechoic fibroids.

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Although still controversial,¹⁻⁵ laparoscopic myomectomy is becoming increasingly more common for treatment of symptomatic intramural myomas.

A logical attempt to make this type of surgery easier and faster is to reduce myoma size and blood flow to the uterus⁶ by preoperative administration of a

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gonadotropin-releasing hormone (GnRH) analog. However, this treatment is reported to increase risk of recurrence,⁷ possibly delay diagnosis of leiomyosarcoma,⁸ increase difficulty finding the cleavage plane,⁹ and cause a greater extent of hyalinization phenomena.¹⁰ Nevertheless, reduction of myoma volume and decreased vascularity of the uterus may be important factors in facilitating laparoscopic myomectomy and improving results.^{11, 12}

Materials and Methods

To assess the ability of ultrasonography to predict fibroids likely to be treated effectively, and to determine the therapeutic efficacy of GnRH analog treatment before laparoscopic myomectomy, we conducted a prospective, randomized study in 74 symptomatic women scheduled for myomectomy. We selected only women in whom the main tumors were intramural and reconstruction of uterine walls with sutures was necessary. This selection was necessary to obtain a homogeneous series of cases of comparable surgical difficulty. The study was approved by the department ethical committee and written, informed consent was provided by each patient.

From September 1994 to July 1996, 74 women with symptomatic uterine fibroids referred to our institutions who fit entry criteria were entered into the trial. Inclusion criteria were history of infertility of more than 3 years or recurrent abortions; symptoms of increased vaginal bleeding, pelvic pain, or pelvic pressure; main myoma not pedunculated, and smaller than 500 cm³ and larger than 4 cm³ on ultrasonography; presence of no more than four myomas; absence of submucosal fibroids on hysteroscopy; absence of ultrasound-documented calcification in the main myoma; absence of hyperplasia with cytologic atypia at endometrial biopsy performed for menometrorrhagia; presence of normal Papanicolaou smear; and negative urine pregnancy test.

At the time of laparoscopy, seven women (2 group A, 5 group B) were excluded because the main myoma was pedunculated or less than 4 cm³ in volume, or because it was associated with severe adhesions or endometriosis. Thus 67 patients (age range 24–45 yrs, mean \pm SD 37.2 \pm 4.0 yrs; parity range of 0–3, mean \pm SD 1.4 \pm 0.6; weight range 55.4–79.6 kg, mean \pm SD 63.6 \pm 4.7 kg) completed the study.

Patients were allocated to one of the two groups according to the same computer-generated random

assignment for both centers. Group A, 35 women, received GnRH analog pretreatment, and group B, 32 women, underwent direct surgery. Surgical equipment was similar in the two centers and the operating surgeon was the same in both centers.

Preoperative Preparation

Women in group A received two intramuscular injections of leuprolide acetate 3.75 mg (Enantone, Takeda, Rome, Italy) 4 weeks apart starting in the luteal phase or within the first 2 days of menses. No side effects of the agent were reported. Laparoscopic myomectomy was performed 2 to 5 weeks after the second injection.

Ultrasound (Aloka Co., Tokyo, Japan) evaluated uterine volume, and number and diameter of myomas with either a 3.5-MHz transabdominal transducer or a 5-MHz transvaginal probe. A pulsed wave Duplex system with the same sector scanner and a high-pass filter of 100 Hz was used to obtain blood flow velocity waveforms of uterine arteries and, when possible, of major vessels supplying identifiable myomas. Peak systole (A) and peak diastole (B) were measured to calculate (A-B/A) the resistance index (RI), taking mean values of three consecutive measurements with a variation coefficient of 2% to 4%.

Echogenicity of the main myoma was evaluated by a relative score of 1 to 7, with 5 equal to isoechogenic to surrounding myometrium. All ultrasonographic determinations were performed on admission of the patient to the study (T0) and in group A immediately before surgery (T1). Preoperative ultrasonographic findings were compared with operative findings.

Operative Procedure

Laparoscopic myomectomy was performed with a 10-mm scope (Karl Storz, Tuttlingen, Germany) with two or three ancillary ports. The first step was to infiltrate the myoma base with up to 20 ml octapressine (Por-8; Sandoz, East Hanover, NJ) 5 IU in 1 ml diluted 1:30, followed by a longitudinal incision as close to midline as possible with unipolar or hook scissors. After the cleavage plane was identified the myoma was enucleated by means of adequate traction with a myoma drill or a strong grasper and countertraction with Manhes forceps, scissors, or hydrodissection instruments. Significant bleeders were coagulated with bipolar forceps and myometrial edges were reapproximated in one or two layers, according to depth of the uterine wound, with 2-0 polyglactin (Ethicon SpA; Pratica di Mare,

Rome, Italy) interrupted figure-of-eight sutures. Myomata were removed in 41 patients with a 15-mm Semm morcellator¹³ (Wisap, Sauerlach, Germany) and in the remaining 26 with a 12-mm Steiner automatic morcellator¹⁴ (Karl Storz).

Operating time was registered. Blood loss was evaluated as the balance between aspirated fluid and irrigation fluid. All tissue samples were submitted for pathologic examination.

Data Analyses

All randomized patients for whom data were available were included in the efficacy analysis. Statistical significance of between-group comparisons was assessed by χ^2 test for proportions. Student's *t* test for paired data was used to compare data between T0 and T1. Student's *t* test for unpaired data was used to compare groups A and B, when appropriate. Duration of operation and intraoperative blood loss were analyzed with the Wilcoxon rank sum test. In all analyses statistical significance was assessed at the 5% level.

Results

The two groups were not different for age, parity, weight, and indications for surgery (Table 1). Uterine volume, number of myomas, diameter of the main myoma, echogenicity of the main myoma, and RIs of uterine arteries and main fibroid vessels were not significantly different between groups at admission (Table 2).

In group A, two injections of GnRH analog significantly reduced uterine volume, and diameter and echogenicity of the main leiomyoma. The number of fibroids identified by ultrasonography was confirmed

at laparoscopy. Preoperative RIs of uterine arteries and main myoma vessels were significantly increased, proving that flow was decreased after leuprolide treatment.

Significant differences between ultrasonographic variables evaluated at admission and operative findings were related to Doppler velocimetry of uterine vessels and main fibroid's major vessels.

Blood loss and operating time were significantly lower in group A ($p < 0.01$ and < 0.05 , respectively; Table 3). Women with more than two myomas and in whom the diameter of the main one was greater than 5 cm had significantly shorter operating time when they were pretreated with a GnRH analog (Table 4). Particularly interesting are surgical correlations of echogenicity of the main myoma. Patients with basal echogenicity of less than 3 had significantly ($p < 0.01$) longer operating time if they received the GnRH analog than the rest of the pretreated women and untreated patients with hypoechoic myomas.

Discussion

Laparoscopic myomectomy is controversial but is becoming more and more common.^{4,15,16} Preoperative administration of a GnRH analog has been advocated in attempts to make surgery easier and faster by reducing myoma size and blood loss. Indeed, studies suggested that such a course (2–3 mo) before laparotomic myomectomy was effective in reducing blood loss,¹⁷ especially in women with uteri larger than 600 cm³.¹⁸ We administered two injections of leuprolide acetate depot instead of three because most reduction in uterine size occurs after approximately 8 weeks of therapy,¹⁹ although a small amount continues for several weeks.²⁰ Furthermore, this short-term treatment should not cause concern about bone loss or hypoestrogenic side effects, and it significantly reduces the cost to patients.

Increased recurrence of myomas associated with GnRH analogs⁷ seems to be related more to the number of fibroids²¹ than to the agents. More important, recurrence is not associated with a greater reoperation rate, cited as low as 10%.¹⁵ Currently, however, no report shows the therapeutic efficacy of GnRH analog treatment before laparoscopic myomectomy.

Regarding ultrasonographic predictors, as expected, when more than two myomas were present and the diameter of the main tumor was greater than 5 cm, operating time improved significantly after

TABLE 1. Patient Characteristics

Characteristic	Group A (n = 35)	Group B (n = 32)
Mean \pm SD age (yrs)	36.8 \pm 4.1	37.7 \pm 3.9
Mean \pm SD weight (kg)	64.4 \pm 4.6	62.8 \pm 4.4
Mean \pm SD parity	1.4 \pm 0.7	1.5 \pm 0.5
Indications for myomectomy, no. (%)		
Abnormal uterine bleeding	15 (42.8)	10 (31.2)
Infertility	8 (22.9)	9 (28.1)
Abortion	7 (20.0)	6 (18.8)
Pain	5 (14.3)	7 (21.9)

None of the values reached significance.

TABLE 2. Ultrasonographic Characteristics (mean \pm SD)

	Group A (n = 35)			Group B (n = 32)
	T0	T0 vs T1	T1	T0
Uterine volume (cm ³)	473 \pm 88	p <0.001	396 \pm 79	458 \pm 92
Number of fibroids	2.1 \pm 0.4		2.1 \pm 0.4	1.9 \pm 0.5
Main fibroid diameter (cm)	4.9 \pm 2.1	p <0.001	4.3 \pm 2.3	4.8 \pm 2.6
Main fibroid echogenicity	5.1 \pm 1.3	p <0.001	3.4 \pm 0.9	4.8 \pm 1.5
RI of uterine arteries	0.66 \pm 0.07	p <0.001	0.79 \pm 0.08	0.63 \pm 0.08
RI of main myomas	0.53 \pm 0.08	p <0.001	0.77 \pm 0.06	0.55 \pm 0.07

T1 group A versus T0 group B, p <0.01 for all values except number of fibroids.

There were no significant differences between groups at T0 for all values.

TABLE 3. Main Outcomes

	Group A (n = 35)	Group B (n = 32)
Mean \pm SD global operating time (min)	98.5 \pm 26.1 ^a	113.3 \pm 35.1 ^a
Mean \pm SD blood loss (ml)	171.8 \pm 70.9 ^b	232.1 \pm 68.1 ^b

^aGroup A versus group B, p <0.05.

^bGroup A versus group B, p <0.01.

TABLE 4. Operating Times as a Function of Ultrasonographic Predictors

Ultrasonographic Predictor	Group A		Group B
Number of myomas			
<3	91.4 \pm 24.0 (24) ^a		99.9 \pm 32.7 (21) ^b
>3	114.1 \pm 24.5 (11) ^a	—a—	139.0 \pm 24.4 (11) ^b
Diameter of main myoma			
<5 cm	86.7 \pm 18.6 (19) ^a		96.7 \pm 28.8 (21) ^c
>5 cm	112.5 \pm 27.3 (16) ^a	—b—	145.0 \pm 21.9 (11) ^c
Echogenicity of main fibroid			
<3	128.3 \pm 17.6 (9) ^c	—a—	114.9 \pm 8.1 (10)
>3	88.2 \pm 20.0 (26) ^c	—a—	112.6 \pm 42.4 (22)

Operating time is in minutes; figures in parentheses are numbers of patients.

^ap <0.05.

^bp <0.01.

^cp <0.001.

GnRH analog therapy. The Doppler velocimetry of uterine vessels and main fibroid's major vessels²² did not correlate with efficacy of pretreatment in reducing operating time. Inversely, for myomata with echogenicity score below 3, the pretreated group had a significantly longer operating time (p <0.05). Given traction maneuvers in laparoscopic myomectomy, difficulty adequately grasping the tumor was the key element in the longer operating time.

Softening of tissue is probably related to degenerative changes induced by GnRH analog pretreatment,¹⁰ particularly in myomas without an adequate fibrous skeleton and thus appearing hypoechoic on ultrasound. Histopathologically, myomas in pretreated women showed a predominance of areas of coagulative necrosis and mixed degeneration. Furthermore, pretreated patients with hypoechoic main fibroids had a longer operating time than all of the rest of the women

with hypoechoic myomas, pretreated and untreated, showing unequivocally the negative effect of GnRH analog pretreatment on this kind of tumor.

Conclusion

Our results show the effectiveness of pretreatment in shortening operating time for myomas larger than 5 cm, in women with multiple myomata, and in complex myomas except hypoechoic lesions. In hypoechoic myomas, GnRH analog reduced tumor density, making enucleation from the uterine walls cumbersome.^{18,23}

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