Gonadotropin-releasing hormone agonist pretreatment did not decrease postoperative adhesion formation after abdominal myomectomy in a randomized control trial

Charles C. Coddington, M.D.,[a,b] *Daniel R. Grow, M.D.,*[c] *Mohamed S. Ahmed, M.D.,*[c] *James P. Toner, M.D., Ph.D.,*[b] *Elizabeth Cook, Ph.D.,*[d] *and Michael P. Diamond, M.D.*[e]

[a] Mayo College of Medicine, Rochester, Minnesota; [b] Eastern Virginia Medical School, Norfolk, Virginia; [c] Baystate Medical Center, Springfield, Massachusetts; [d] University of Massachusetts, Amherst, Massachusetts; and [e] Wayne State University School of Medicine, Detroit, Michigan

Objective: To determine if 3 months of preoperative gonadotropin-releasing hormone agonist (GnRH-a) treatment decreases postoperative uterine adhesions after open abdominal surgery for the removal of uterine fibroids.
Design: Prospective, randomized, clinical study.
Setting: A tertiary care medical center.
Patient(s): Women of reproductive age with symptomatic uterine fibroids not amenable to hysteroscopic removal.
Intervention(s): Twenty patients underwent an initial abdominal myomectomy followed by a second-look laparoscopy for evaluating uterine adhesions after random allocation to groups receiving either GnRH analog or placebo for 3 months before the initial surgery.
Main Outcome Measure(s): Adhesion formation between treatment groups and by incision number and aggregate length.
Result(s): Presurgical GnRH-a treatment did not decrease adhesion formation compared with placebo. For every additional centimeter of incision length, the total adhesion area over the uterine serosal surface increased by 0.55 cm^2. The number of myomas removed and the number of incisions were positively correlated with total adhesion area.
Conclusion(s): Preoperative treatment with GnRH-a for 3 months before open abdominal myomectomy did not decrease postoperative uterine adhesions. Following the standards of good surgical technique, adhesions are minimized with fewer and smaller incisions. (Fertil Steril® 2009;91:1909–13. ©2009 by American Society for Reproductive Medicine.)

Key Words: Myoma, fibroid, myomectomy, adhesions, adhesion prevention

Adhesion formation after obstetric and gynecologic surgery is common. In studies of patients with prior surgery, adhesions may occur in as many as 80% of cases as a result of the surgical procedure (1). Although the number of patients who will require reoperation is small (2), it is significant. Adhesions can also cause many symptoms such as pain, nausea, vomiting, dysmenorrhea, and dyspareunia (2). Adhesions after uterine myomectomy are particularly disturbing in infertility patients; adhesions involving the uterus and fallopian tubes may cause infertility, when paradoxically the surgery was performed for fertility enhancement.

In studies involving uterine surgery in cynomolgus monkeys, it has been demonstrated that postoperative utero-omental adhesions were reduced when preoperative therapy with gonadotropin-releasing hormone agonist (GnRH-a) was used to produce a state of hypo-estrogenism (3). This is consistent with prior reports that have demonstrated that estrogen and progesterone both promote angiogeneisis and growth factor production in female reproductive tissues (4, 5) and that pelvic adhesions have estrogen and progesterone receptors (6). Additionally, estrogen deprivation causes an decrease in uterine blood flow, (7, 8), and hypoestrogenism causes fibroids to shrink by approximately 40% after 3

Received October 20, 2007; revised and accepted February 15, 2008; published online April 25, 2008.

Study sponsored in part by TAP Pharmaceuticals (Chicago IL) through a grant to C.C.C.

D.R.G. has nothing to disclose. E.C. owns investments in Warner Chilcott and Accelent. M.P.D. has received research grants from Serono, Ethicon, and Boehringer Ingleheim; is a consultant for Genzyme, Omrix, and Neomend; and is a stockholder in Advanced Reproductive Care. C.C.C. has nothing additional to disclose. M.S.A. has nothing to disclose. J.P.T. has nothing to disclose.

Reprint requests: Daniel Grow, M.D., Baystate Medical Center, Department of Obstetrics and Gynecology, 759 Chestnut Street, Springfield, MA 1199 (FAX: 413-784-8166; E-mail: daniel.grow@bhs.org).

0015-0282/09/$36.00
doi:10.1016/j.fertnstert.2008.02.128

months of GnRH-a therapy; thus, incision size would be expected to be smaller (8–10). Changes in the coagulation system, including plasminogen activator, plasminogen activator inhibitor, and matrix metalloproteinase, may also affect the mechanism of adhesion formation (11).

Mechanisms by which presurgical GnRH-a therapy might reduce postoperative adhesion development after fibroid surgery would include decreased stimulation of sex steroid receptors, decreased uterine blood flow, and decreasing fibroid size. Our study tested this hypothesis in a clinical context using a standard clinical approach. We treated women undergoing a laparotomy for myomectomy with GnRH-a in a randomized, double-blind, prospective, concurrent, controlled trial to determine if there would be a reduction of postsurgical adhesions when surgery was performed in a hypoestrogenic state.

MATERIALS AND METHODS

Twenty reproductive-age women who were undergoing surgery for symptomatic uterine leiomyomata were randomly assigned to complete 3 months of preoperative depot GnRH-a therapy (Lupron, 3.75 mg monthly; TAP Pharmaceuticals, Chicago, IL) or placebo (saline) every 28 days for three doses before their surgery by laparotomy. Surgery was performed within 4 weeks of the final injection. All patients desired uterine preservation. A clinical nurse supervised randomization and monitored diaries and symptoms to ensure that patient concerns were addressed and to keep the treating physicians blinded to the patient's treatment status. The protocol was approved through the Eastern Virginia Medical School institutional review board.

The surgical approach was similar for each patient and included the same senior surgeon (C.C.C.) in all cases. After the laparotomy was performed using a Pfannesteil incision, the abdomen was assessed for adhesions. All pelvic adhesions were characterized with respect to area (cm^2) and type. After the initial assessment was made, the area over the myoma to be incised was injected with a dilute pitressin (1 vial or 20 units per 20 mL of saline) solution. The myometrium was incised with a knife; the myoma was identified and grasped with a tenaculum. Dissection was performed around the myoma until a stalk was created. The stalk was cross-clamped, cut and tied with O-Chromic. The myoma was measured and weighed after being passed from the field.

The defect thus created was closed with interrupted O-Chromic suture on a CT-1 or CT-2 needle. Once the defect was closed, the serosa was closed with a baseball-stitch of 4-O Vicryl. Any bleeding vessel was either cauterized with a needle-tip Bovie or ligated with a figure-of-eight stitch of 4-O Vicryl. All myomas that were seen or palpated were removed. Closure of the parietal peritoneum was performed with 4-O Vicryl in an interrupted fashion with a minimal number of sutures. A careful log was maintained for each procedure to include length of each incision, incision location, and the size, weight, and number of myomas removed. The patients were allowed to recover in a standard fashion.

Two to 10 weeks later, patients underwent a second-look laparoscopic surgery to evaluate and measure the adhesions present. Adhesions were resected or disrupted, sharply or bluntly, during the grading procedure as clinically appropriate. For each adhesion as they could be best separated, the length and width was measured by a graded probe or ruler to ensure accuracy. Location of the adhesions and the relationship to prior uterine incisions were noted and recorded in the log for each procedure. The same senior surgeon (C.C.C.) performed all adhesion scoring and was blinded to the treatment group of the patients. All procedures were videotaped, and measurements confirmed by an external reviewer.

We used linear regression modeling to analyze the relationship between a number of variables, namely, total number of myomas, number of myomas removed/incision, average total incision length per patient (cm), number of incisions into uterus, second-look adhesion area (cm^2), and a ratio of adhesion area (cm^2) to total myometrial incision length (cm) (A/L ratio). Second-look adhesion area (cm^2) was defined as the surface of uterine visceral peritoneum covered with adhesions. Total myometrial incision length was defined as the total length of all incisions made through the uterine visceral peritoneum through which myoma removal occurred.

All statistical analyses were performed using STATA 8.0 (STATA Corporation, College Station, TX). We used Student's *t*-test to examine differences in mean values of continuous variables for patients in the treatment and placebo groups. The results from these bivariate analyses were used to build a series of multivariable linear regression models to explore the impact of key independent variables on adhesion area. Variables were eliminated from consideration if they were not statistically significant and did not confound the relation between adhesion area and the other covariates remaining in the models.

RESULTS

All 20 patients who were randomized to participate in the study completed the prescribed therapy and underwent a laparotomy for myomectomy. A second-look laparoscopy to measure, evaluate, and remove adhesions was performed on 19 patients. There were no complications requiring readmission and no known infectious complications.

Two women in the placebo group were excluded from the analysis (ID = patients 6 and 10). The first patient (ID 10) had severe pelvic adhesive disease at the time of the myomectomy procedure, a great contrast with the other study patients, so she was prospectively excluded from the data analysis because of the concern that adhesion assessment at second-look laparoscopy would likely be confounded by a large amount of adhesion reformation. The second patient (ID 6) had no myoma removed from the uterus at the time of the initial procedure. This woman was found to have adenomyosis at laparotomy, was excluded from the study, and did not have a second-look procedure.

Among the women who received GnRH-a, several became pseudo-menopausal and had symptoms of hypoestrogenism, as has been reported by our study and others (9).

The adhesion area increased as the cumulative length of the uterine incisions increased, as shown in Figure 1. There were no statistically significant differences in adhesion area at the second-look procedure between the GnRH-a group and the placebo group.

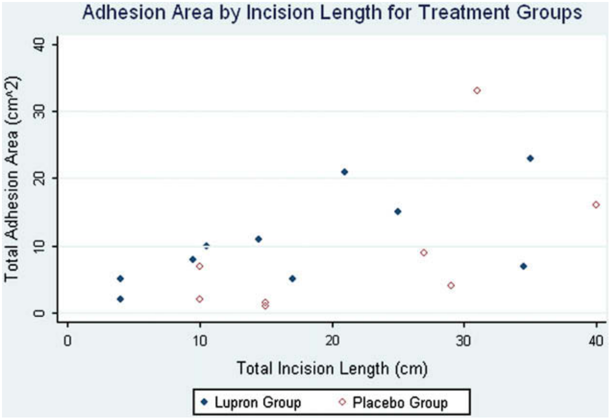
The summary data for number of myomas removed, incision length, number of incisions, initial adhesion area, second-look adhesion area, and total adhesion area/total incision length ratio (A/L ratio) are presented in Table 1. The groups were no different for number of myomas removed, average incision length, initial-look adhesion area, or second-look adhesion area. A statistically significant difference noted between the groups in a calculated A/L ratio (P=.05), with the placebo group having fewer adhesions per centimeter of uterine incision length than the GnRH-a group.

Careful recording of surgical parameters, which were reviewed by an external reviewer and confirmed, allowed mathematical modeling of adhesion formation. Table 2 presents the coefficients, standard errors, and P values for three linear regression models for total adhesion area. Total adhesion area was positively associated with cumulative length of uterine incisions (P=.013, variance = 0.36), allowing the simplest model, Model 1:

$$\text{Adhesion area} = 1.36 + 0.44 \times \text{Incision length}$$

FIGURE 1

Regression plot showing that as total incision length into the uterus increases the resultant area of the uterus involved with adhesions also increases (as observed at second-look laparoscopy).



Coddington. Adhesions linked to uterine incisions. Fertil Steril 2009.

Although the association between the number of myomas removed and total adhesion area was not statistically significant, inclusion of this variable in the model had an important impact on the coefficient for incision length, indicating that the number of myomas removed is an important confounder of the association between incision length and total area. For this reason, both variables were considered when modeling adhesion area in Model 2:

$$\text{Adhesion area} = 1.67 + 0.55 \times \text{Incision length} - 0.35 \times \text{Number of myomas removed}$$

As the number of incisions was also positively correlated with total adhesion area, a third model was generated that considered the impact of adding this variable to a model including incision length and number of myomas removed. The result is Model 3:

$$\text{Adhesion area} = 2.43 + 0.59 \times \text{Incision length} - 0.16 \times \text{Number of myomas removed} - 0.57 \times \text{Number of incisions}$$

DISCUSSION

The hypothesis of this study, that GnRH-a pretreatment before abdominal myomectomy would decrease postoperative adhesion formation to the uterine serosa, was not proven correct. Control patients who received placebo injections instead of leuprolide acetate not only had fewer side effects (vasomotor symptoms) but also had lesser adhesion area per centimeter of incision length into the uterus than the treatment group. The overall adhesion area was not different between the two groups.

The use of carefully monitored second-look surgical evaluations has enabled the quantitative study of the genesis and prevention of postsurgical adhesions, though most of these studies have been performed in rodent models. Human studies involving a second-look procedure for adhesion prevention are rare because of the difficulty in obtaining consent, as there is no good evidence of a direct patient benefit. Likewise, the timing of the second-look procedure has not been well established in the literature. It is generally believed that adhesion formation occurs in the first 3 to 5 days after an operation (12). Adjuvants to prevent adhesions such as absorbable barriers and peritoneal coatings and solutions take advantage of this belief. The timing of the second-look procedure (2 to 10 weeks) was scheduled to consider both patient convenience, study logistics, and the expectation that the adhesions formed would be mature enough to be considered permanent.

Our study provides a unique data set. We based our work on initial animal work with cynomolgus monkeys who were treated and reevaluated for adhesions. In the monkey studies, the GnRH analog use demonstrated a reduction of adhesions. This effect was further enhanced when barrier methods were used as well (Interceed and Gore-Tex) (3). In

TABLE 1

Results of surgical measurements and adhesion characteristics collected during the initial myomectomy procedure and the subsequent second-look adhesion evaluation procedure for the 18 patients who met criteria for data analysis (mean SE).

	3-month depo Lupron	Placebo	*P* value
Number of patients	10	8	
Total number of myomas/patient	6.2 (1.4)	7.5 (1.8)	.57
Initial look adhesion area to uterus (cm^2)	0.4 (0.1)	0.4 (0.1)	.98
Number of myomas removed/incision	1.2 (0.1)	1.4 (0.2)	.51
Average total incision length per patient (cm)	17.5 (3.6)	22.1 (3.9)	.40
Number of incisions into uterus	4.8 (0.8)	5.1 (0.9)	.79
Second-look adhesion area (cm^2)	10.7 (2.2)	9.2 (3.8)	.72
Area/length ratio	0.7 (0.1)	0.4 (0.1)	.05

Coddington. Adhesions linked to uterine incisions. Fertil Steril 2009.

addition, other animal studies have suggested that a hypoestrogenic environment may lead to decreased adhesion formation (13). Thus, our study was a logical stepping stone to the study of adhesion prevention.

Though adhesion area overall was not statistically different between the two groups, patients randomized to receive 3 months of preoperative GnRH-a had an increased adhesion area/incision length (A/L ratio, $P=.05$). This was an unexpected finding as GnRH-a is known to shrink fibroids and thus was likely to reduce incision length. Fibroids after GnRH-a administration are sometimes more difficult to extract from the surrounding compressed myometrium (the pseudo-capsule). The increased manipulation of the incision site can result in additional peri-incisional trauma and potentially can result in more adhesions. But from another theoretical point of view, the 40% reduction in myoma size seen after GnRH-a therapy may decrease the adhesions because the incision length would be notably decreased (9, 10).

The randomization schedule appears to have been effective for making the comparison groups similar. The groups were similar for number of fibroids removed per patient, number of fibroids removed per incision, and for total incision length. One might expect that the total incision length in the GnRH-a group would be slightly smaller because of medically related fibroid size reduction, but this difference did not reach statistical significance.

TABLE 2

Three models for adhesion area (n = 18).

Model	Variable	Coefficient	Standard error	*P* value
1	Adhesion area = 1.36 + 0.44 × Incision length			
	Constant	1.36	3.6	.708
	Incision length	0.44	0.2	.013
2	Adhesion area = 1.67 + 0.55 × Incision length – 0.35 × Number of myomas removed			
	Constant	1.67	3.7	.655
	Incision length	0.55	0.2	.033
	Number of myomas removed	−0.35	0.6	.537
3	Adhesion area = 2.43 + 0.59 × Incision length – 0.16 × Number of myomas removed − 0.57 × Number of incisions			
	Constant	2.43	4.3	.578
	Incision length	0.59	0.3	.041
	Number of myomas removed	−0.16	0.8	.837
	Number of incisions	−0.57	1.5	.710

Note: The results in Table 2 for Model 2 can be interpreted to mean that for every additional 1 cm of incision length, the total adhesion area increases by 0.55 cm^2 (assuming that the number of myomas remains constant). Conversely, if the incision length is constant, removing multiple myomas through the same incision length decreases adhesion area.

Coddington. Adhesions linked to uterine incisions. Fertil Steril 2009.

Changes in the coagulatory and fibrinolytic responses, which may theoretically favor the limitation of permanent adhesion formation, have been associated with Gn-RH-a (14). Though serum levels of coagulation factors and fibrin degradation products were not measured in our study, the lack of clinical effect on adhesion prevention in the GnRH-a group may suggest that other effects of the surgical process were more influential in developing adhesions. The ease of fibroid removal from the surrounding myometrium, for example, has been suggested to be more difficult when fibroids shrink in response to GnRH-a. This was not measured or included in our evaluations. Although GnRH-a may have an effect on the reduction of postoperative blood loss, this end point was not rigorously measured (15).

Detailed and systematic recording of the incision site, length, myoma numbers, and adhesion characteristics has allowed further insight into the genesis of adhesion formation after myomectomy procedure. First, we have confirmed the expected: adhesion area increases as incision length into the uterus increases. Our study has quantified the impact of uterine surface disruption, specifically, for every centimeter of incision into the uterus, approximately 0.44 cm^2 of adhesion was observed to form (Table 2, Model 1).

In mathematical modeling, Model 2 implies that as the incision length is held constant, so removing additional myomas from the uterus may actually decrease adhesion area. This makes clinical sense only when multiple myomas are easy to remove from an established incision and if additional uterine serosal trauma can be avoided. This would seem to statistically confirm an age-old tenet: removing multiple myomas from the same incision is beneficial if that incision length is kept to a minimum (16, 17).

Additional modeling (Model 3) suggested that, if the incision length and the number of myomas removed remained constant, then the uterus with the more numerous but smaller individual incisions would have less adhesion area. Clinically, keeping incision length to a minimum while placing incisions at the location of individual myomas(as opposed to extending incisions to capture multiple myomas) would appear to be sound surgical judgment.

We found that GnRH-a pretreatment for 3 months before myomectomy did not decrease adhesion formation as had been predicted. The most important predictor of adhesion formation in this myomectomy study was the incision length into the uterine surface. As total incision length into the uterus increased, adhesions to the uterine serosa increased. Methods to decrease incision length, such as removing multiple fibroids from the same incision to decrease peritoneal injury, seem to reduce adhesion formation.

REFERENCES

1. Perry JF, Smith GA, Yonehiro EG. Intestinal obstruction caused by adhesions: a review of 388 cases. Ann Surg 1955;142:810–6.
2. Ray NF, Denton WG, Thamer M, Henderson SC, Perry S. Abdominal adhesiolysis: Inpatient care and expenditures in the United States in 1994. J Am Coll Surg 1998;186:1–9.
3. Grow DR, Coddington CC, Hsiu JG, Mikich Y, Hodgen GD. Role of hypoestrogenism on sex steroid antagonist in adhesion formation after myometrial surgery in primates. Fertil Steril 1996;66:140–7.
4. Herve MA, Meduri G, Petit FG, Domet TS, Lazennec G, Mourah S, Perrot-Applanat M. Regulation of the vascular endothelial growth factor (VEGF) receptor Flk-1/KDR by estradiol through VEGF in uterus. J Endocrinol 2006;188:91–9.
5. Walter LM, Rogers PA, Girling JE. The role of progesterone in endometrial angiogenesis in pregnant and ovariectomised mice. Reproduction 2005;129:765–77.
6. Wiczyk HP, Grow DR, Adams LA, O'Shea DL, Reece MT. Pelvic adhesions contain sex steroid receptors and produce angiogenesis growth factors. Fertil Steril 1998;69:511–6.
7. Achiron R, Lipitz S, Frenkel Y, Mashiach S. Endometrial blood flow response to estrogen replacement therapy and tamoxifen in asymptomatic, postmenopausal women: a transvaginal Doppler study Ultrasound. Obstet Gynecol 1995;5:411–4.
8. Aleem FA, Predanic M. The hemodynamic effect of GnRH agonist therapy on uterine leiomyoma vascularity: a prospective study using transvaginal color Doppler sonography. Gynecol Endocrinol 1995; 9:253–8.
9. Coddington C, Collins R, Showker T, Anderson R, Loriaux L, Winkel C. Long acting gonadotropin releasing hormone analog used to treat uteri. Fertil Steril 1986;45:624–8.
10. Letteri G, Coddington C, Winkel C, Showker T, Loriaux L, Collins R. Efficacy of gonadotropin releasing hormone agonist in treatment of uterine leiomyomata. Fertil Steril 1989;51:951–7.
11. Sharpe-Timms KL, Zimmer RL, Jolliff WJ, Jolliff WJ, Wright JA, Nothnick WB, et al. Gonadotropin-releasing hormone agonist (GnRH-a) therapy alters activity of plasminogen activators, matrix metalloproteinases, and their inhibitors in rat models for adhesion formation and endometriosis: potential GnRH-a-regulated mechanisms reducing adhesion formation. Fertil Steril 1998;69:916–23.
12. diZerega GS, Campeau JD. Peritoneal repair and post-surgical adhesion formation. Hum Reprod Update 2001;7:547–55.
13. Freeman ML, Saed GM, Diamond P. Hormone Independent Ovarian Influence on Adhesion Development. Fertil Steril 2002;78:340–6.
14. Winkler U, Buhler K, Koslowski S, Oberhoff C, Schindler AE. Plasmatic haemostasis in gonadotropin-releasing hormone analogue therapy: effects of leuprolide acetate depot on coagulatory and fibrinolytic activities. Clin Ther 1992;14:114–20.
15. Falsetti L, Mazzani MD, Rubessa S, Ruggeri C. Presurgical treatment of uterine fibroids by using gonadotropin-releasing hormone agonists. Acta Eur Fertil 1992;23:29–32.
16. Bonney V. Abdominal myomectomy. In: Berkeley AS, Bonney V, eds. A Textbook of Gynecological Surgery. 5th ed. New York: Paul B Hoeber, 1948. J Endocrinol. 2006;188:91–9.
17. Bonney V. The technique and results of myomectomy. Lancet 1931; 220:171.