# Comparison of surgery alone and combined surgical-medical treatment in the management of symptomatic uterine adenomyoma

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**Objective:** To compare the efficacy of surgical-medical treatment and surgery alone in the treatment of uterine symptomatic adenomyoma.
**Design:** Prospective nonrandomized study.
**Setting:** Medical centers.
**Patient(s):** One hundred sixty-five women treated with conservative adenomyomectomy.
**Intervention(s):** Surgery followed by six-course treatment (n = 114, surgical-medical group) or no treatment (n = 51, surgery-alone group) with a gonadotropin-releasing hormone (GnRH) agonist regimen.
**Main Outcome Measure(s):** Symptom relief (scale: 0, no symptoms, to 5, worst symptoms) and relapse (when any one scale was $\geq$2 after treatment) during the 2-year follow-up period.
**Result(s):** The general characteristics of the patients were similar in both groups, except for the diameter of the adenomyoma and age. Patients in both groups had statistically significant symptom relief, and all symptom scores declined from a mean of 3 or 4 to a mean of 1 or less at the end of the 2-year follow-up period. The symptom-relapse rates in the surgical-medical group were statistically significantly lower than those in the surgery alone group (n = 32, 28.1% vs. n = 25, 49.0%, respectively).
**Conclusion(s):** Conservative surgery, regardless of GnRH agonist treatment, may be acceptable for management of a selected population with severe symptomatic adenomyoma. However, surgical-medical treatment provided more effective symptom control (a lower symptom relapse rate) than surgery alone during the 2-year follow-up period. (Fertil Steril® 2009;92:876–85. ©2009 by American Society for Reproductive Medicine.)

**Key Words:** Adenomyoma, conservative surgery, gonadotropin-releasing hormone agonist, surgical-medical management

Uterine adenomyoma differs from uterine adenomyosis due to its relatively localized characteristics (i.e., focal adenomyosis) or its related disease, adenomyosis. The most common symptoms of uterine adenomyoma, while insufficient for diagnosis, are dysmenorrhea, menorrhagia, and chronic pelvic pain (1). These diseases sometimes coexist with other gynecologic pathologies and are most often associated with endometriosis. Treatment with different strategies has been tried (2). Any conservative treatment is a first choice when preservation of fertility is desired. Unfortunately, treatment options based on such symptoms have been variably effective, with the result that it is still difficult to manage symptomatic patients. For refractory patients who prefer conservative measures and also decline hysterectomy, the treatment options are ill-defined.

Among the conservative treatments, medical therapy may be the least invasive and most acceptable strategy, and includes the use of prostaglandin inhibitors, oral contraceptive pills, progestogens, danazol, gestrinone, and gonadotropin-releasing hormone (GnRH) agonists (3–10). Unfortunately, the effect of these medical treatments is often transient; and the symptoms (especially pain) of uterine adenomyoma-related diseases nearly always reappear after discontinuing medication (1).

Although surgical therapy may be a mainstay for treating symptomatic adenomyoma-related disease, conservative surgical intervention is seldom considered to play a role in managing patients who would like to preserve their future fertility. Selecting a good candidate for this approach can be difficult—how does one determine the extent of adenomyosis tissue in a particular patient group (adenomyoma)? Furthermore, conservative surgery may not completely clear

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adenomyoma, as it occasionally involves the whole uterus diffusely (adenomyosis), and separating normal myometrial tissue from myometrial tissue invaded by adenomyoma can be difficult (2, 11). In addition, postoperative sequelae such as pelvic adhesion cannot be completely avoided. Finally, the possibility of uterine rupture should be considered, because excising the adenomyoma (adenomyomectomy) might be more difficult and more complicated than excising the leiomyoma (myomectomy) (2).

However, the surgical approach for preserving the uterus can be considered when dysmenorrhea does not respond to drug treatment, the patient cannot tolerate the side effects of long-term drug treatment, or the patient wants to have a definite diagnosis. The standard conservative surgical approach has been excision of the myometrial adenomyoma through exploratory laparotomy, but the results have been varied (12, 13). The development of advanced techniques has led to other, less invasive conservative surgical approaches, including endomyometrial ablation, laparoscopic myometrial electrocoagulation, and laparoscopic surgery (14–17). In addition, uterine artery embolization has also been available in the management of women with adenomyoma or adenomyosis (18–23). All conservative surgical treatments have been proven effective in up to 50% of patients (12–15); however, the follow-up assessment periods have been of short duration (12–15, 17).

Due to the transient effect of medical therapy and the only 50% effectiveness of surgical therapy in managing uterine adenomyoma-related diseases, the combination of conservative surgery and medical treatment either with a GnRH agonist or with danazol (surgical-medical treatment) has been developed. The early results have been promising and welcome (11, 16, 24, 25).

Because either conservative surgery alone or surgical-medical treatment is reported to be therapeutic for symptomatic uterine adenomyoma-related diseases, the question arises as to whether it is necessary to add a six-course postoperative GnRH agonist in the management of women with symptomatic uterine adenomyoma who have been treated with conservative surgery. Our observational study addressed this question by assessing the necessity of a postoperative GnRH agonist in the management of women with symptomatic uterine adenomyomas who have been treated with conservative surgery.

## MATERIALS AND METHODS

### Participants

The procedures used in this study were in strict accordance with the guidelines of the Helsinki Declaration on human experimentation, and the protocol was approved by the institutional review board. The aim of the protocol was first explained to all prospective participants; thereafter, written informed consent was obtained from those actually enrolled in the study.

Participants were eligible for the study if they were between 20 and 45 years of age. If they had severe dysmenorrhea with or without menorrhagia and a firm, enlarged uterus, they were given a tentative diagnosis of uterine adenomyoma and/or possible adenomyosis. The preoperative evaluation included a routine biochemistry workup, complete blood count, and ultrasound examination. All patients received both transvaginal and abdominal ultrasound evaluations with the exception of patients who denied having ever had a sexual experience, who were evaluated by abdominal ultrasound only. The typical ultrasound findings, including uterine enlargement (26), asymmetrical thickening of the anterior or posterior myometrial wall (26), heterogeneous, poorly circumscribed areas within the myometrium (27, 28), anechoic lacunae or cysts of varying size (27), and increased echotexture of the myometrium, were highly indicative of the possibility of the presence of adenomyoma.

Because there is no uniform agreement on the most appropriate therapeutic methods for managing symptomatic uterine adenomyoma when the women want to preserve their uterus, these women were informed that they could choose to be treated with any one of the following therapies, based on their willingness and preference. Therapies included the use of medical therapy such as pills, danazol, a GnRH agonist, gestrinone, and nonsteroidal anti-inflammatory drugs; uterine-sparing surgical therapies such as adenomyomectomy (conservative surgery), which could be performed through traditional exploratory laparotomy, minilaparotomy, ultraminilaparotomy, laparoscopy, or any combination of these therapies; or a definite curative surgical therapy with hysterectomy if fertility was completed or the patient did not insist on uterine preservation. If patients selected conservative surgery as their preference, they were extensively counseled regarding possible surgical risks, current and future benefits, and the curative nature and fertility issues related to such conservative surgeries because the postoperative uterine function and fertility status after conservative surgery are not well-known.

Postoperatively, patients could choose any one or a combination of the following therapies: pure follow-up, GnRH agonist therapy, hormone therapies other than a GnRH agonist, or any medication for symptom relief or well-being.

The diagnosis of the adenomyoma was confirmed by final pathology. Patients with other significant diseases of the pelvic organs, and/or other medical or surgical illnesses were excluded. Patients with the following diseases also were excluded: [1] medical or other chronic illness (e.g., anemia due to other causes, including hereditary anemia, blood loss from the upper or lower gastrointestinal tracts by stool routine and history [no occult blood), liver, renal, endocrine, or metabolic disorders, or poor nutrition status]; [2] a coexistence of extensive pelvic or uterine diseases (e.g., extensive endometriosis, ovarian endometriomas, or endometriosis associated with obliteration of the cul-de-sac, or hydrosalpinx, extensive pelvic adhesion, pelvic inflammatory diseases, or multiple uterine fibroids).

Because our study was conducted to assess the necessity of the use of GnRH agonist in the management of women with symptomatic uterine adenomyomas who had been treated with conservative therapy, only women treated with conservative surgery alone or conservative surgery plus six courses of postoperative GnRH agonists (surgical-medical treatment) were enrolled into the study. All patients were evaluated regularly for at least 2 years after completing therapy. The final analysis comprised 165 women.

### Surgical Treatment

Minilaparotomy (29, 30), ultraminilaparotomy (31, 32), or laparoscopy (33, 34) was used with these patients. The principles of reproductive surgery were strictly followed, thereby minimizing trauma to normal uterine tissue at all times (11). Microsurgical techniques were applied, including magnification, intermittent irrigation, and fine atraumatic instrumentation to decrease blood loss and prevent postoperative adhesion formation (35).

The adenomyotic lesions were meticulously dissected, and careful removal of all non-microscopic lesions was ensured by a systematic and thorough palpation of the uterus. The surgical margins were electrocauterized to destroy all residual lesions, and pelvic adhesions were excised. To decrease bleeding, a routine local injection of 10 mL diluted 80× vasopressin (20 IU/mL vasopressin added to 80 mL of isotonic sodium chloride) was administered at the site of adenomyoma. In those cases in which the uterine cavity was entered, 2-0 poliglecaprone 25 (Monocryl; Ethicon, Somerville, NJ) was used for closure.

In addition, the tubal ostia were visualized using the following strategy, if appropriate, including a splint that was inserted in both the uterine cavity and the fimbriae (36) or a retrograde dye (a methylene blue saline solution) injection that was used to demonstrate the os of the bilateral tubal ostia when accidentally entering the uterine cavity, so as to avoid iatrogenic injuries.

Horizontal sutures followed by locking sutures were used to close the myometrium, leaving as little dead space as possible. The serosa was closed with a continuous inverting suture of 5-0 poliglecaprone 25 (Monocryl; Ethicon) to minimize raw surfaces on the uterus, which was covered by an adhesion-prevention barrier (oxidized regenerated cellulose, ORC; Interceed; Johnson & Johnson Medical Inc., Arlington, TX), if appropriate. Finally, copious peritoneal irrigation with a 1:10,000 dilution of heparin-containing lactated Ringer's solution was used to clean the debris and blood clots within the abdominal cavity (37).

Postoperatively, the patients received a six-course monthly regimen of GnRH agonist therapy (Leuplin-Depot; Takeda Pharmaceuticals, Osaka, Japan) or follow-up examinations without any other hormone therapies, based on their willingness and preference.

### Assessment of Treatment Response

Dysmenorrhea was defined as pelvic pain during, shortly before, or after menstrual periods. The periods were restricted to the two most recent cycles of menstruation at the time of the visit. Because assessing the level of pain in an individual can be difficult (38), most clinical studies of pain use standardized methods that are not used in clinical practice (38), such as the Visual Analog Scale (rating pain from "none" to "worst ever") (39–41), the McGill Pain Questionnaire (42), or a unique simple categorical scale (43). Quality of life scales, such as the SF-36, also are used to assess the impact of pain and the response to treatment (44). In this study, we did not use the above-mentioned standardized methods to evaluate variation in pelvic pain; rather, we used a self-reported 6-point verbal numeric rating scale (VNRS-6; modified with the Visual Analog Scale, VAS) and the Analgesic Usage Score (AUS), which is a modified pain scale originally developed by Biberoglu et al. (43) and Andersch et al. (45). The VNRS-6 is an easy-to-use scale for the evaluation of pain and has a high correlation with the VAS (33). The patient was asked to identify how much pain she was having by choosing a number from 0 (no pain) to 5 (the worst pain imaginable).

The AUS, based on analgesic use, was recorded simultaneously. Absolutely no analgesics needed was scored as 0; an occasional one or two analgesic drugs needed during menstruation (less than 1 day) was scored as 1; $\geq 3$ analgesic drugs needed during menstruation (less than 3 days) was scored as 2; analgesic drugs needed during the entire course of menstruation was scored as 3; analgesic drugs needed during menstruation and occasionally during intermenstruation days was scored as 4; and analgesic drugs needed nearly every day was scored as 5. The AUS system also showed a high correlation with the VAS and was consistent with the analysis of the VNRS-6 (33).

To evaluate the menorrhagia of these patients, another simple-to-use scale system was developed. This system was a combination of subjective and objective evaluations based on the Mansfield-Voda-Jorgensen Menstrual Bleeding Scale (MVJ) and anemia (46–48). The subjective menstrual period was modified by the MVJ, against an objective measure, such as the weight of used menstrual products (46). The MVJ was used to estimate the total quantity of menstrual fluid discharge. This Likert-type scale was developed by the investigators for use by participants who were keeping menstrual diaries. The 6-point scale ranged from 1 (spotting) to 6 (gushing) and was based on the participant's perception of how often she would need to change a product (not how often she actually does). In addition, because the relationship between anemia and menstrual blood loss has been noted before (47, 48), hemoglobin levels were used as an objective evaluation. Therefore, this menorrhagia scale system was a subjective-menstrual-period-and-objective-hemoglobin scale system, which was defined as a bleeding episode persisting for more than 7 days in each cycle, and a hemoglobin level of less than 10 g/dL without other causes of anemia.

Menorrhagia was graded by the duration of menses and degree of anemia: no anemia and menses lasting less than 4 days was scored at 0; no anemia and menses lasting between 4 and 7 days was scored at 1; no anemia and menses lasting more than 1 week was scored at 2; anemia and menses lasting less than 4 days was scored at 3; anemia and menses lasting between 4 and 7 days was scored at 4; and anemia and menses lasting more than 7 days was scored at 5.

Ultrasound was used as an evaluation tool in this study. With the exception of patients who denied having ever had a sexual experience who were evaluated by abdominal ultrasound only, all patients received simultaneous abdominal and transvaginal ultrasounds, which were also performed annually during the follow-up period. Magnetic resonance imaging (MRI) was not used routinely because the cost was high and it was not covered by the National Health Insurance Bureau (NHIB) in Taiwan.

The study goal was to determine symptom relief and symptom relapse after conservative surgery with or without GnRH-agonist treatment in the management of women with symptomatic uterine adenomyoma. Symptom relapse was defined as when any VNRS-6, AUS, or menorrhagia scale was $\geq 2$ or more severe ($\geq 3$) during the follow-up period. The threshold of 2 for relapse was based on the patients asking for medical treatment because of prolonged menstruation or dysmenorrhea that required more analgesic drugs for pain relief.

### Follow-Up Procedures

Every 4 months after complete therapy (the operative date in the control group, and the last dose of GnRH-agonist treatment in the surgical-medical group), for a period of at least 2 years, the patients' menstrual symptoms (i.e., dysmenorrhea and menorrhagia) were recorded. Scores for pain (dysmenorrhea) and menorrhagia were completed before and after the operation, then every 4 months with at least eight regular follow-up visits. Transvaginal and abdominal ultrasounds were used annually during then follow-up period, and reproductive outcomes were recorded.

### Statistical Analysis

Statistical analysis was performed using SPSS for Windows (version 11.5; SPSS Inc., Chicago, IL). Mean was compared by *t*-test, and proportions were compared by chi-square or Fisher's exact tests. Paired *t*-tests were used for changes of each score from baseline. $P<.05$ was considered statistically significant.

## RESULTS

Our analysis included 165 women, after we had excluded 36 women: 29 with extensive pelvic or uterine disease and 7 with medical or other chronic illness. The surgery-alone group comprised 51 women (30.9%) who selected regular follow-up evaluations without any other hormone therapy. The surgical-medical group comprised 114 women (69.1%) who received the complete six-course GnRH-agonist treatment.

The characteristics of the women who were analyzed are shown in Table 1. Seven patients were evaluated by abdominal ultrasound only, and the remaining 158 patients received both transvaginal and abdominal ultrasound evaluations at the beginning of the study. Compared with the women in the surgical group, patients in the surgical-medical group were slightly older, had a slightly higher degree of menorrhagia at baseline, and had larger maximal diameters of adenomyoma (Table 1). After treatment, at the end of the first year, the patient pain scores for dysmenorrhea (i.e., the VNRS-6) showed a statistically significant decline from the baseline (pretreatment) of $3.94 \pm 0.43$ to $0.39 \pm 0.52$ in the surgical-medical group, and from $3.86 \pm 0.51$ to $0.51 \pm 0.56$ in the control group (data presented as mean $\pm$ standard deviation; both $P<.001$). At the end of the second year, the patients' pain scores were $0.78 \pm 0.84$ in the surgical-medical group and $1.14 \pm 0.87$ in the control group (both $P<.001$) (Table 2).

The AUS also showed similar findings for both groups. The AUS declined statistically significantly from $2.77 \pm 0.97$ to $0.23 \pm 0.37$ in the surgical-medical group and from $2.67 \pm 0.85$ to $0.24 \pm 0.37$ in the control group at the end of the first year (both $P<.001$), and to $0.56 \pm 0.70$ in the surgical-medical group and $0.80 \pm 0.66$ in the control group at the end of the second year (both $P<.001$). Taken together, the data suggest that both treatments effectively relieved the dysmenorrhea symptoms of the patients, in that the severity of dysmenorrhea declined during this 2-year follow-up period (see Table 2).

In addition to the dramatic relief of dysmenorrhea, menorrhagia in both groups also showed statistically significant improvement at the end of the first year, with scores dropping from the baseline of $3.68 \pm 1.03$ to $0.43 \pm 0.54$ in the surgical-medical group and $3.08 \pm 1.44$ to $0.63 \pm 0.64$ in the control group (both $P<.001$); at the end of the second year, they were $0.91 \pm 0.77$ in the surgical-medical group and $1.27 \pm 1.14$ in the control group (both $P<.001$). These data show that both treatments effectively relieved the menorrhagia symptoms of patients during the 2-year follow-up period (see Table 2).

Consistent with the statistically significant improvement in the menorrhagia symptoms of patients during the follow-up period, anemia status, as predicted, also showed statistically significant improvement in both groups (see Table 2). Both groups at 12 months after treatment showed increased hemoglobin levels at $12.1 \pm 1.6$ g/dL in the surgical-medical group versus $11.8 \pm 1.8$ g/dL in the surgery-alone group compared with $9.2 \pm 1.4$ g/dL at the baseline in the surgical-medical group and $9.7 \pm 1.7$ g/dL at the baseline in the surgery-alone group, respectively (both $P<.01$).

We did not use imaging data (ultrasound) to define symptom relapse because suspicious relapses (recurrence) as

**TABLE 1**

**Baseline characteristics of the enrolled women.**

| | Surgical-medical (n = 114) | Surgery alone (n = 51) | *P* value |
|---|---|---|---|
| Age (years) | 38.9 ± 3.8 | 37.0 ± 4.8 | .039 |
| Body mass index (kg/m$^2$) | 23.0 ± 1.6 | 23.0 ± 2.0 | .956 |
| Preoperative CA 125 | 58.9 ± 27.6 | 56.3 ± 26.4 | .665 |
| Baseline Hgb (g/dL) | 9.2 ± 1.4 | 9.7 ± 1.7 | .102 |
| Adenomyoma location | | | .897 |
| Anterior wall % (n) | 14.0% (16) | 17.6% (9) | |
| Posterior wall % (n) | 74.6% (85) | 70.6% (36) | |
| Fundal area % (n) | 11.4% (13) | 11.8% (6) | |
| Maximal diameter (mm) | 55.3 ± 12.1 | 48.8 ± 10.9 | .008 |
| Operation | | | .837 |
| Mini % (n) | 36.8% (42) | 35.3% (18) | |
| Ultramini % (n) | 52.6% (60) | 51.0% (26) | |
| Laparoscopy % (n) | 10.5% (12) | 13.7% (7) | |
| Symptom | | | |
| Menorrhagia | 3.68 ± 1.03 | 3.08 ± 1.44 | .020 |
| VNRS-6 | 3.94 ± 0.43 | 3.86 ± 0.51 | .482 |
| AUS | 2.77 ± 0.97 | 2.67 ± 0.85 | .577 |

*Notes:* Data are presented as mean ± standard deviation. Hgb: hemoglobin; mini: minilaparotomy; Surgical-medical: conservative surgery followed with six-course gonadotropin-releasing hormone agonist; ultramini: ultramini laparotomy; VNRS-6 and AUS: self-reported 6-point verbal numeric rating scales and Analgesic Usage Score.

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detected by ultrasound (e.g., reappearance of a uterine mass) were very low in both groups, which made it difficult to analyze (data not shown). As mentioned previously, to determine effectiveness after conservative surgery with or without GnRH-agonist treatment, we needed to evaluate the flare-up of symptoms in the patients during the follow-up period. Therefore, we assessed the symptoms using the scoring system as a tool for evaluation. Using the

**TABLE 2**

**Patient characteristics during follow-up period.**

| | Group | Baseline | 12 months | 24 months | P1 | P2 |
|---|---|---|---|---|---|---|
| VNRS-6 | S+M | 3.94 ± 0.43 | 0.39 ± 0.52 | 0.78 ± 0.84 | <.001 | <.001 |
| | S-alone | 3.86 ± 0.51 | 0.51 ± 0.56 | 1.14 ± 0.87 | <.001 | <.001 |
| AUS | S+M | 2.77 ± 0.97 | 0.23 ± 0.37 | 0.56 ± 0.70 | <.001 | <.001 |
| | S-alone | 2.67 ± 0.85 | 0.24 ± 0.37 | 0.80 ± 0.66 | <.001 | <.001 |
| Menorrhagia | S+M | 3.68 ± 1.03 | 0.43 ± 0.54 | 0.91 ± 0.77 | <.001 | <.001 |
| | S-alone | 3.08 ± 1.44 | 0.63 ± 0.64 | 1.27 ± 1.14 | <.001 | <.001 |
| Hemoglobin (g/dL) | S+M | 9.2 ± 1.4 | 12.1 ± 1.6 | 11.5 ± 1.1 | <.001 | <.001 |
| | S-alone | 9.7 ± 1.7 | 11.8 ± 0.8 | 10.8 ± 1.5 | <.001 | <.001 |
| Relapse (≥2) | S+M | 114 (100%) | 7 (6.1%) | 32 (28.1%) | <.001 | <.001 |
| | S-alone | 51 (100%) | 7 (13.7%) | 25 (49.0%) | <.001 | <.001 |
| Relapse (≥3) | S+M | 114 (100%) | 1 (0.9%) | 14 (12.3%) | <.001 | <.001 |
| | S-alone | 51 (100%) | 1 (2.0%) | 12 (23.5%) | <.001 | <.001 |

*Notes:* Data are presented as mean ± standard deviation. P1: comparison between baseline and 12 months; P2: comparison between baseline and 24 months; Relapse: symptom relapse; S-alone: conservative surgery alone; S+M: surgical-medical treatment, conservative surgery followed with six-course gonadotropin-releasing hormone agonist; VNRS-6 and AUS: self-reported 6-point verbal numeric rating scales and Analgesic Usage Score.

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**TABLE 3**

**Therapeutic outcomes of women treated with conservative surgery with or without gonadotropin-releasing hormone agonist at the end of the 2-year follow-up period.**

| | Surgical-medical (n = 114) | Surgery alone (n = 51) | *P* value |
|---|---|---|---|
| Hemoglobin (g/dL) | 11.5 ± 1.1 | 10.8 ± 1.5 | .024 |
| Symptom | | | |
| Menorrhagia | 0.91 ± 0.77 | 1.27 ± 1.14 | .101 |
| VNRS-6 | 0.78 ± 0.84 | 1.14 ± 0.87 | .049 |
| AUS | 0.56 ± 0.70 | 0.80 ± 0.66 | .084 |
| Relapse (≥2) | 32 (28.1%) | 25 (49.0%) | .009 |
| Relapse (≥3) | 14 (12.3%) | 12 (23.5%) | .067 |
| Reproductive outcome | Surgical-medical (n = 44) | Surgery alone (n = 27) | |
| Term | 61.4% (n = 27) | 55.6% (n = 15) | .631 |
| Preterm | 11.4% (n = 5) | 7.4% (n = 2) | .590 |
| Abortion | 6.8% (n = 3) | 11.1% (n = 3) | .531 |
| Successful delivery | 72.7% (n = 32) | 63.0% (n = 17) | .391 |
| Clinical pregnancy | 79.5% (n = 35) | 74.1% (n = 20) | .595 |

*Notes:* The follow-up time was extended in some cases (up to 7 months) to evaluate the final reproductive outcome. Clinical pregnancy: the sum of successful delivery and abortion. Surgical-medical: conservative surgery followed with six-course gonadotropin-releasing hormone agonist; Relapse: symptom relapse; Successful delivery: the sum of term and preterm; VNRS-6 and AUS: self-reported 6-point verbal numeric rating scales and Analgesic Usage Score.

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threshold of 2 or 3, we found that 57 and 26 women, respectively, had symptom relapses during the 2-year follow-up period.

Consistent with the different evaluation variables shown, patients in either the surgical-medical group or the surgery-alone group showed a lower relapse rate (6.1% or 0.9% of the surgical-medical group and 13.7% or 2.0% of the surgery-alone group) at the end of the first year (all $P<.001$), and the therapeutic effects could be maintained up to 2 years (all $P<.001$) (see Table 2). In addition, symptom control in the surgical-medical and surgery-alone groups was similar, using a threshold of 2 or 3 at the end of the first year ($P=.132$ and $P=.524$, respectively), suggesting that conservative surgery, regardless of GnRH-agonist treatment, might provide acceptable symptom control in patients with symptomatic adenomyoma.

To clarify the value of adjuvant GnRH agonist, Table 3 summarizes the therapeutic outcomes of both groups at the end of the 2-year follow-up period. The data showed a similar therapeutic effect for both the surgical-medical and surgery-alone treatment. Many of the evaluation variables, including the menorrhagia scale, AUS, and symptom relapse rate (threshold of 3), showed no statistically significant difference. However, hemoglobin levels, the VNRS-6, and the symptom relapse rate (threshold of 2) showed a more apparent improvement in patients who were treated with surgical-medical therapy (see Table 3), suggesting that surgical-medical treatment provided more definitely effective symptom control than surgery alone during the 2-year follow-up period.

In terms of reproductive outcomes, 71 of the 165 patients (44 in the surgical-medical group and 27 in the surgery-alone group) were sexually active and did not use contraception (see Table 3). Fifty-five women became pregnant, with a clinical pregnancy rate of 77.5%, and 49 women (69.0%) had a successful delivery by the end of the 2-year follow-up period, which included additional months (up to 7 months) to evaluate the final reproductive outcome. Between the surgical-medical group and the surgery-alone group, there was no statistically significant difference in either clinical pregnancy rate (79.5% vs. 74.1%, respectively) or successful delivery rate (72.7% vs. 63.0%, respectively). Seven women (14.3%) had a diagnosis of preterm labor and were treated with various kinds of tocolytic medications, either as an outpatient or with hospitalization (see Table 3).

Table 4 shows the differences in demographics and clinical characteristics at baseline and therapy between the women who had and did not have a symptom relapse at the end of the 2-year follow-up period. Compared with the women who did not have a symptom relapse at the 24-month follow-up period, the women who had a symptom relapse had a statistically significantly higher preoperative serum CA125 level ($P<.001$), higher baseline menorrhagia scales ($P<.001$), higher baseline VNRS-6 ($P<.001$), and higher baseline AUS ($P=.032$). Neither age nor body

**TABLE 4**

**Characteristics of the women with symptom relapse (≥2) at the end of the 2-year follow-up after treatment.**

| | Relapse (n = 57) | Without relapse (n = 108) | *P* value |
|---|---|---|---|
| Age (years) | 37.7 ± 5.4 | 38.6 ± 5.0 | .240 |
| Body mass index (kg/m$^2$) | 23.4 ± 1.9 | 22.8 ± 2.0 | .336 |
| Preoperative CA125 | 81.3 ± 42.3 | 45.9 ± 24.4 | <.001 |
| Baseline Hgb (g/dL) | 9.3 ± 1.9 | 9.4 ± 1.8 | .715 |
| Adenomyoma location | | | .724 |
| Anterior wall | 36% (9) | 64% (16) | |
| Posterior wall | 32.5% (43) | 64.5% (70) | |
| Fundal area | 26.3% (5) | 73.7% (14) | |
| Maximal diameter (mm) | 52.4 ± 14.8 | 53.8 ± 14.4 | .566 |
| Operation | | | .513 |
| Mini | 35.0% (21) | 65.0% (39) | |
| Ultramini | 35.7% (35) | 64.3% (63) | |
| Laparoscopy | 14.3% (1) | 85.7% (6) | |
| Symptom | | | |
| Menorrhagia | 4.23 ± 1.17 | 3.10 ± 1.43 | <.001 |
| VNRS-6 | 4.32 ± 0.71 | 3.70 ± 0.48 | <.001 |
| AUS | 3.40 ± 1.13 | 2.39 ± 0.94 | .032 |
| Treatment | | | .009 |
| Surgical-medical treatment | 28.1% (32) | 71.9% (82) | |
| Surgery alone | 49.0% (25) | 51.0% (26) | |

*Notes:* Surgical-medical treatment: conservative surgery followed by six-course gonadotropin-releasing hormone agonist; mini: minilaparotomy; ultramini: ultraminilaparotomy; VNRS-6 and AUS: self-reported 6-point verbal numeric rating scales and Analgesic Usage Scores.

*Wang. Surgical treatment for uterine adenomyoma. Fertil Steril 2009.*

mass index was related to symptom relapse. In addition, tumor size and location were also not related to symptom relapse.

## DISCUSSION

Providing those who have adenomyoma with relief from dysmenorrhea and menorrhagia is the principle goal of therapy. Most patients with this disease have completed childbearing and seek definitive therapy, so hysterectomy has always been considered the standard treatment for severe adenomyoma-related diseases refractory to medical intervention. However, due to the recent trend toward organ-preserving surgery and delayed pregnancy (49–52), the number of women with adenomyoma-related diseases who wish to retain their uterus is on the rise. In addition, there is still no consensus on the optimal therapeutic approach with which to manage adenomyoma in the symptomatic patient who desires to retain her uterus. Therefore, we undertook this prospective nonrandomized study to compare conservative surgery alone and the combination of conservative surgery and six-course GnRH-agonist treatment in patients who were undergoing treatment for symptomatic uterine adenomyomas.

The strong evidence documenting estrogen, progesterone, and androgen receptor involvement and decidual reactions in adenomyotic foci implies that ectopic endometrium is in fact hormone-responsive, suggesting a possible role for hormonal manipulation in the treatment of adenomyoma-related diseases (53). Indeed, GnRH agonist has been used for the treatment of adenomyoma-related diseases, resulting in both a reduction in uterine size and symptomatic improvement. However, the effect of GnRH-agonist treatment is often transient, and nearly all patients experience symptoms and signs after discontinuing the therapy. More effective treatment is required. Conservative surgery such as adenomyomectomy might be an alternative.

The rationale for the use of conservative surgery with adenomyomas is based on the relatively localized adenomyosis tissue within the uterus. Laparoscopic electrosurgical myolysis in patients with adenomyoma-related diseases has been described by Phillips et al. (15) with relatively promising results in a small cohort. Seven of 10 women treated with three courses of GnRH agonist after myolysis continued to have complete resolution or significant reduction of their symptoms at 12 months (15). The study by Wood et al. (14). found that four of seven women treated in a similar fashion

experienced prolonged relief of symptoms. The same report also involved myometrial resection in the instance of localized adenomyosis (adenomyoma); seven of eight women experienced a long-term reduction in both menorrhagia and dysmenorrhea (1, 14).

In our study, conservative surgery, regardless of medical treatment, effectively relieved the severity of the symptoms in women with adenomyoma-related diseases, as demonstrated not only by the patient pain scores (VNRS-6 and AUS) but also by the patient menorrhagia scales at the end of the first year. In addition, symptom improvement continued into the second year even though the therapeutic effect showed little decline compared with the end of the first year. Symptoms were dramatically improved in both groups, which resulted in the finding that more than 95% of patients reported they were satisfied with the treatment at the end of the first year, and more than 90% of patients were satisfied with the treatment (93.9%, n = 155) at the end of the second year.

In terms of symptom relapse, the original symptoms or signs were correlated with symptom relapse at the end of the 2-year follow-up period because our patients with symptom relapse had higher preoperative CA125 levels, higher menorrhagia and dysmenorrhea scores, and a larger adenomyoma size. However, these parameters should be applied with caution in routine clinical practice, especially CA125 serum levels, as it was not clear which parameter could be used for the assessment of the severity of patients with uterine adenomyoma or endometriosis (54). In addition, CA125 levels might not be universally acceptable in the assessment of patients with pelvic pain because the correlation between pelvic pain and CA125 levels has been poor in studies of endometriosis (55, 56). Furthermore, the value of CA125 in predicting recurrence (relapse) after conservative surgical treatment for endometriosis is questionable (57, 58).

Our surgical-medical group had a statistically significantly lower symptom relapse rate than the surgery-alone group, suggesting that surgical-medical treatment could provide longer durable symptom control than surgery alone. We found that more than 70% of patients in the surgical-medical group were free of symptoms at the end of the 2-year follow-up period; by contrast, only 50% of patients in the surgery-alone group remained free of symptoms.

Although our study suggests the benefit of a six-course GnRH agonist in the management of women with symptomatic uterine adenomyomas who were undergoing conservative surgery, many limitations could not be avoided. First, clearly, the two groups are not well matched, which is an expected compromise when there is no randomization. Patients in the surgical-medical group were older, had higher menorrhagia scale scores, and had larger adenomyoma diameters compared with those in the surgery-alone group. This might have interfered with the outcome evaluation. For example, younger age has often been reported as a risk factor for future recurrence of endometriosis (59, 60), and the age in the surgery-alone group was younger. This also might have contributed to the higher symptom-relapse rate in the surgery-alone group. By contrast, tumor size is also an important independent factor for future recurrence of endometriosis (58); the tumor size was statistically significantly bigger in our surgical-medical group, but the symptom-relapse rate was lower in that group. Second, we treated patients based on their preferences and willingness. However, the cost of GnRH agonists and adhesion prevention material are not covered by the NHIB in Taiwan, so this extra self-paid expense for the patients might have further compromised the validation of the outcome measures. Third, only patients who completed a 2-year follow-up after treatment were enrolled for analysis, so selection bias could not be avoided. Nevertheless, our study represents real-world practice.

Imaging tools, such as ultrasound and MRI, were not used as a regular means to define symptom relapse, but they could add more reliable information during follow-up evaluation, and they have been widely used in the majority of studies (18–23, 61–63); thus, "reappearance of adenomyoma" was not clear in our study. Four reasons led us to not use such more reliable criteria, especially MRI, in the evaluation of the patients for "recurrence" or "relapse." First, only a low percentage of patients in both groups showed a reappearance of a uterine mass (less than 5% in both groups). Second, MRI is not covered by the NHIB for this indication (follow-up of patients with symptomatic adenomyoma after treatment) in Taiwan, so the patients would have had to pay for it themselves. Third, we did not know the actual diagnoses of these recurrent uterine masses (adenomyoma, fibroids, or others) because we could not get tissue for pathology proof. Forth, the goal of our study was to evaluate the therapeutic effect after conservative surgery with or without GnRH-agonist treatment in the management of women with symptomatic uterine adenomyoma by assessing symptom relief and relapse. Thus, we used a scoring system to define symptom relapse: when any VNRS-6, AUS, and menorrhagia grade was $\geq 2$ during the follow-up period. We defined 2 ($\geq 2$) as the threshold for symptom relapse partly because these patients might need medical care—for example, more analgesic drugs for symptom control of prolonged days of menstruation—and partly because there was an adequate sample size (n = 57) for analysis (28.1% of the surgical-medical group vs. 49.0% of the surgery-alone group, $P$=.009). This strategy, although it requires confirmation, might provide useful and practical information when evaluating the therapeutic outcomes of these patients because the true diagnosis of uterine adenomyoma is always retrospective (11); the treatment options should focus on adequate symptom relief, if these patients want uterine preservation.

Finally, the impact on the reproductive outcomes of the women with symptomatic adenomyoma after conservative surgery, regardless of adjuvant GnRH-agonist treatment, seemed to be acceptable: nearly 70% (49 of 71) of patients had successful deliveries. This was consistent with the report by Fedele et al. (12). The incidence of preterm labor in our

study was 14.3% (7 of 49), which was higher than in the general population in Taipei City (9%), seemed consistent with or even lower than the 18% among women with a diagnosis of adenomyoma or adenomyosis in our previous study (64). This suggests that conservative surgery, regardless of GnRH-agonist treatment, in the management of women with symptomatic adenomyoma might not increase the preterm labor rate compared with outcomes for women with a suspected or confirmed diagnosis of uterine adenomyoma.

Our results indicate clearly the effectiveness of conservative surgery, regardless of GnRH agonist treatment, in the management of women with symptomatic uterine adenomyomas. However, surgical-medical treatment provided more effective symptom control compared with surgery alone during our 2-year follow-up period.

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