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Original Article

Reproductive performance of severely symptomatic women with uterine adenomyoma who wanted preservation of the uterus and underwent combined surgical–medical treatment

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Abstract

Objective: To assess the factors associated with future pregnancy and successful delivery in women who were treated for uterine adenomyoma with combination (surgical–medical) therapy using ultramini- or mini-laparotomy conservative surgery and gonadotropin-releasing hormone agonist.

Materials and Methods: One hundred and two women were evaluated. Items for analysis included: age, body mass index, and conception history; clinical symptoms of dysmenorrhea and menorrhagia; tumor location and preoperative serum level of cancer antigen 125 (CA125); the intraoperative findings of the weight of the removed tumor, and the uterine cavity opening.

Results: After excluding those patients using contraception or searching for an assisted reproductive technique, a total of 56 women were enrolled for analysis. Twenty-three (41.1%) women had 27 clinical pregnancies after 3 years of follow-up; 15 went on to deliver a healthy live-born child; two delivered preterm but healthy babies; seven had elective abortions; four had spontaneous abortions; and one had an ectopic pregnancy. The women who had a successful delivery during the 3-year follow-up after treatment tended to be younger, with a lower body mass index, lower baseline analgesic usage score, and lower preoperative serum level of CA125, be nulliparous, and with an adenoma in an anterior location. The linear regression model showed that age and baseline analgesic usage score were independent predictors of successful delivery and accounted for 56.5% of the total variance related to successful delivery.

Conclusion: Age was an important factor associated with future successful delivery, therefore, caution should be taken in considering the maintenance of future fertility in older women treated with surgical–medical therapy.

Keywords: adenomyoma; conservative surgery; fertility; gonadotropin-releasing hormone agonist; mini-laparotomy

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Introduction

Uterine adenomyosis and its variant uterine adenomyoma (relatively localized characteristics of focal adenomyosis) not only present dysmenorrhea, menorrhagia, and chronic pelvic pain, but also may contribute to subfertility [1–4]. Hysterectomy is often considered the optimal treatment for uterus-related pathology, including adenomyosis, adenomyoma, myoma, and other diseases [5–9]. In addition, adenomyosis or adenomyoma penetrate into the normal myometrium diffusely, rendering their complete removal difficult and the possibility of recurrence high [10–12]. However, many women with uterine pathology have a strong desire to preserve the uterus, for which alternative treatment options are available [13–17].

Among these options, medical therapy, which may be the least invasive and most acceptable strategy, includes the use of prostaglandin inhibitors, oral contraceptive pills, progestogens, danocrine, and gonadotropin-releasing hormone (GnRH) agonist [18–21]. Unfortunately, the effect of these medical treatments is often transient and some patients cannot tolerate the side effects of long-term medical treatment; furthermore, the symptoms (especially pain) of uterine adenomyoma nearly always reappear when discontinuing medication [2].

For those who are refractory to or unsuitable for long-term medical treatment, conservative surgical approaches, including endomyometrial ablation, laparoscopic myometrial electrocoagulation, laparoscopic cytoreductive surgery, and excision of the myometrial adenomyoma through exploratory laparotomy, have been tried, although they are considered to be more invasive and radical treatments [22–24]. It is disappointing that the effects have been varied, and the highest effective rate was reported to be 50%. In addition, and of most importance, follow-up assessment has been of short duration and the long-term effect is not clear, although one report showed a successful pregnancy outcome in one patient [23].

As a result of the transient effect and possible poor compliance with medical therapy, and the only 50% effectiveness of the above-mentioned surgical approaches in managing uterine adenomyoma, the combination of conservative surgery and medical treatment with either GnRH agonist or danazol (surgical–medical treatment) has been tried [24–28]. The current study was a further follow-up of 102 women with uterine adenomyoma treated with a combination of ultramini- or mini-laparotomy conservative surgery and six courses of GnRH agonist [28]. Our goal was to focus on the fertility outcome of patients who did not receive reproductive assistance.

This may be one of the largest series to search for the critical factors related to the future pregnancy rate of patients who receive combination (surgical–medical) treatment for adenomyoma.

Materials and methods

Patients

The detailed information of this study has been published before [28]. The protocol was first explained to all prospective participants after the institutional review board approval; thereafter, written informed consent was obtained from those actually enrolled in this 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 comprised a routine biochemistry workup, including cancer antigen 125 (CA125) in the luteal phase of every woman, complete blood count, and ultrasound examination. All patients received both transvaginal and abdominal ultrasound evaluations, with the exception of patients who denied ever having had a sexual experience, who were evaluated by abdominal ultrasound only.

The diagnosis of 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 endometrioma, or endometriosis associated with obliteration of the cul-de-sac, hydrosalpinx, extensive pelvic adhesion, pelvic inflammatory diseases, or multiple uterine fibroids). The exclusion criteria were use of a contraception method, searching for an assisted reproductive technique, and laparoscopic surgery for removal of adenomyoma.

Our study was conducted to determine the factors associated with the future pregnancy and successful delivery of women with uterine adenomyoma who were treated with a combination of ultramini- or mini-laparotomy conservative surgery and GnRH agonist therapy. Therefore, only women treated with this combination therapy who intended to become pregnant after treatment, and who were not using a contraception method or searching for an assisted reproductive technique were enrolled into the study. All patients were evaluated regularly for at least 3 years after completing therapy. The final analysis comprised 56 women.

Combined surgical–medical treatment

Ultramini- or mini-laparotomy was used in all surgical procedures [29–32]. The principles of reproductive surgery were strictly followed, thereby minimizing trauma to normal uterine tissue at all times [33–35]. The microsurgical technique was applied, including magnification, intermittent irrigation, and fine atraumatic instrumentation to decrease blood loss and prevent postoperative adhesion formation. The adenomyotic lesions were meticulously dissected, and careful removal of all nonmicroscopic lesions was assured by 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 40–80× vasopressin (20 IU/mL

vasopressin added to 40–80 mL 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, USA) was used for closure. The tubal ostia were visualized using the following strategy: a splint was inserted in both the uterine cavity and the fimbriae and a retrograde dye (a methylene blue saline solution) injection was used to demonstrate the os of the bilateral tubal ostia when accidentally opening 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 a raw surface on the uterus. Finally, copious peritoneal irrigation with a 1:10,000 dilution of heparin-containing lactated Ringer's solution was used to clean debris and blood clots within the abdominal cavity.

All patients received a six-course monthly regimen of GnRH agonist therapy (Leuplin-Depot; Takeda Pharmaceuticals, Osaka, Japan) postoperatively. The first dose was given to all patients at the beginning of the first postoperative menstrual cycle. Postoperative, rather than preoperative administration of GnRH agonist was chosen to facilitate the intraoperative identification of adenomyotic lesions and to suppress progression of residual lesions postoperatively.

Assessment of severity of dysmenorrhea and menorrhagia

Dysmenorrhea was defined as pelvic pain during, shortly before, or after menstrual periods. The periods were restricted to the two most recent attacks of menstruation at the time of the visit. To evaluate variation in pelvic pain, we used a self-reported six-point verbal numeric rating scale (VNRS-6). When using the VNRS-6, the patients were asked to rate their pain on a scale from 0 to 5, where 0 represented "no pain" and 5 "the worst pain possible", using whole numbers (6 integers including zero). Clinical practice of pain scores (analgesic usage score: AUS) based on analgesic use were also recorded, with absolutely no analgesics needed scored at 0; an occasional one or two analgesic drugs needed during menstruation (<1 day) scored at 1; ≥3 analgesic drugs needed during menstruation (<3 days) scored at 2; analgesic drugs needed during the entire course of menstruation scored at 3; analgesic drugs needed during menstruation and occasionally during intermenstruation days scored at 4; and, analgesic drugs needed nearly every day scored at 5.

Menorrhagia was defined as a bleeding episode persisting for >7 days in each cycle, and a hemoglobin level <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 <4 days was scored at 0; no anemia and menses lasting for 4–7 days was scored at 1; no anemia and menses lasting >1 week was scored at 2; anemia and menses lasting <4 days was scored at 3; anemia and menses lasting 4–7 days was scored at 4; anemia and menses lasting > 7 days was scored at 5.

Follow-up procedures

After completion of GnRH agonist therapy, the patients' pregnancy rate and outcome were recorded for a period of at least 3 years.

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 11.5 (SPSS Inc., Chicago, IL, USA). Descriptive statistics (mean value ± standard deviation) and (*n* and %) are shown in Table 1. The association between dichotomous and categorical variables was examined with χ^2 or Fisher's exact tests. The Student *t* test was used to compare means of continuous variables. Stepwise linear regression models were then fit, including all of the variables of interest at the same time as independent variables, to enable us to demonstrate the relative contribution of each of these variables to the outcome variables. Significance was set at $p < 0.05$ for all tests using a two-tailed α.

Results

A total of 56 women were enrolled for analysis. The symptoms were significantly improved after this combined surgical–medical treatment for uterine adenomyoma. For example, the VNRS-6 and AUS were significantly reduced during the follow-up period: VNRS-6 from the baseline of 3.96 ± 0.41 to 0.32 ± 0.46, 0.68 ± 0.78, and 1.27 ± 1.22 at the end of the 1st year, 2nd year, and 3rd year, respectively ($p < 0.001$) and AUS from 2.71 ± 1.03 to 0.29 ± 0.42, 0.50 ± 0.63, and 1.02 ± 0.92 at the end of the first year, second year, and third year, respectively ($p < 0.001$) (Table 1).

Twenty-three (41.1%) patients had 27 clinical pregnancies after 3 years of follow-up. The outcomes included 13 term

Table 1
Clinical characteristics of the patients who were analyzed.

	n = 56
Age (mean ± SD)	38.3 ± 4.6 years
Body mass index (mean ± SD)	21.0 ± 2.0
Parity	
0	22 (39.3%)
1	30 (53.6%)
2	4 (7.1%)
Baseline VNRS-6 (mean ± SD)	3.96 ± 0.41
Baseline AUS (mean ± SD)	2.71 ± 1.03
Baseline menorrhagia scores (mean ± SD)	3.73 ± 0.98
Anemia	46 (82.1%)
Preoperative serum level of CA125	70.3 ± 32.0 U/mL
Localization of adenomyoma during operation	
Anterior	18 (32.1%)
Posterior	30 (53.6%)
Fundal	8 (14.3%)
Removed adenomyoma weight (mean ± SD)	177.6 ± 64.0
Cases with entry into the uterine cavity	17 (30.4%)

AUS = analgesic usage score; CA125 = cancer antigen 125; SD = standard deviation; VNRS-6 = six-point verbal numeric rating scale.

infants, two preterm infants, seven elective abortions, four spontaneous abortions, and one ectopic pregnancy (Table 2).

To report the factors associated with successful live births, we divided the 56 women into two groups: Group A ($n = 15$) containing 13 term infants and two preterm infants, and Group B ($n = 41$) containing the others, including the remaining 12 clinical pregnancies. Compared to the women who did not have a successful delivery, the women who had a successful delivery had a significantly younger mean age, lower body mass index, low baseline self-reported VNRS-6 (3.7 vs. 4.0), low baseline AUS, low preoperative serum level of CA125, higher proportions of null parity, and an anterior location of the adenoma (Table 3).

These significant variables during the univariate analysis were subsequently included in the multivariate linear regression model. The regression model showed that age and baseline AUS were independent predictors of successful delivery during the 3-year follow-up (Table 4). This model accounted for 56.5% of the total variance related to successful delivery, and yielded an equation: successful delivery $= 2.64 + (-0.054) \times$ age $+ (-0.112) \times$ baseline AUS.

Many of the pregnancies ($n = 7$) ended as elective termination during the 3-year follow-up, and in order to avoid a significant bias in predicting future fertility, therefore, these patients who were treated with elective termination may be considered as "supposed" successful fertility. Therefore, we redivided the 56 women into two new groups: Group C ($n = 19$) containing 13 term infants, two preterm infants, and seven elective abortions, and Group D ($n = 37$) containing the others, including the remaining five clinical, but definitely unsuccessful pregnancies. The women who had supposed successful pregnancies had significantly lower tumor weight and tended to be nulliparous. The linear regression model showed that tumor weight alone accounted for 16.1% of the total variance of supposed successful pregnancies ($\beta = -0.002$, standard error $= 0.001$, $p = 0.002$) (Table 5).

Discussion

Adenomyoma (relatively localized characteristics of focal adenomyosis) is one of the two forms in which adenomyosis can present, and consists of circumscribed nodular aggregates of endometrial glands and stroma within the myometrium [2]. Providing those who have adenomyoma with relief from severe dysmenorrhea and menorrhagia is the principal goal of therapy in the current study (mean of the VNRS-6 of the study population was 3.96, indicating these patients suffered from severe painful menstruation). All enrolled patients had undergone various kinds of medical treatment before but none of them achieved satisfactory symptom control. In addition, many patients had completed childbearing, and therefore sought definitive therapy. Therefore, hysterectomy has always been considered the standard treatment for these severely symptomatic patients with adenomyoma refractory to medical intervention. However, due to the recent trend toward organ-preserving surgery and delayed pregnancy, the number of women diagnosed with adenomyoma who wish to maintain their uterus is on the rise.

One important study has reported that conservative surgery for adenomyoma is associated with a favorable reproductive prognosis [12]. Although medical treatment is always considered as the first choice for these severely symptomatic patients with adenomyoma who desire to retain fertility, and the surgical approach is considered as a more invasive and radical method, there is still no consensus on the optimal therapeutic

Table 2
Pregnancy outcomes following combined surgical–medical treatment of adenomyoma in patients not using contraception ($n = 56$) with follow-up intervals.

	1 y	2 y	3 y	Total
Term deliveries	7	4	2	13
Preterm deliveries	1	1	0	2
Spontaneous abortions	2	1	1	4
Elective terminations	2	3	2	7
Ectopic pregnancies	0	0	1	1
Pregnancies	12	9	6	27

Follow-up began after completion of gonadotropin-releasing hormone agonist therapy.

Table 3
Comparison of the demographics and clinical characteristics at baseline between the women who had or did not have a successful delivery during follow-up.

	Group A	Group B	p
	Women who had a successful delivery ($n = 15$)	Women who did not have a successful delivery ($n = 41$)	
Age (mean ± SD)	32.1 ± 3.6	40.6 ± 4.1	<0.001
BMI (mean ± SD)	19.3 ± 1.6	21.6 ± 2.4	0.002
Baseline VNRS-6 (mean ± SD)	3.7 ± 0.5	4.0 ± 0.7	0.09
Baseline AUS (mean ± SD)	2.0 ± 0.5	3.0 ± 1.3	<0.001
Menorrhagia score (mean ± SD)	3.6 ± 1.4	3.8 ± 1.4	0.66
CA125 (mean ± SD)	34.4 ± 11.8	83.4 ± 42.5	<0.001
Tumor weight (g)	165.0 ± 63.0	182.2 ± 90.6	0.50
Nulliparity	10 (67%)	12 (29%)	0.01
Location			
Anterior	9 (60%)	9 (22%)	0.025
Posterior	5 (33%)	25 (61%)	
Fundal	1 (7%)	7 (17%)	
Entering cavity	3 (20%)	14 (34%)	0.51

AUS = analgesic usage score; BMI = body mass index; CA125 = cancer antigen 125; SD = standard deviation; VNRS-6 = six-point verbal numeric rating scale.

Table 4
Results of stepwise multivariate linear regression analysis of the associations between successful delivery, demographics, and clinical characteristics.

	β	Standard error of β	Explained variance	p
Age	−0.054	0.007	0.476	<0.001
Baseline AUS	−0.112	0.034	0.089	0.002

AUS = analgesic usage score.

Table 5
Comparison of the demographics and clinical characteristics at baseline between the women who had or did not have supposed successful pregnancies during follow-up.

	Group C	Group D	*p*
	Women who had a supposed successful pregnancy ($n = 19$)	Women who did not have a supposed successful pregnancy ($n = 37$)	
Age (mean ± SD)	37.3 ± 4.6	38.8 ± 5.8	0.359
BMI (mean ± SD)	21.1 ± 2.3	20.9 ± 2.6	0.868
Baseline VNRS-6 (mean ± SD)	3.9 ± 0.7	4.0 ± 0.6	0.858
Baseline AUS (mean ± SD)	2.9 ± 1.5	2.6 ± 1.1	0.545
Menorrhagia score (mean ± SD)	3.6 ± 1.6	3.8 ± 1.3	0.76
CA125 (mean ± SD)	80.6 ± 51.0	65.7 ± 38.4	0.234
Tumor weight (gm)	127.1 ± 41.1	199.6 ± 88.6	<0.001
Nulliparity	10 (58.8%)	12 (30.8%)	0.048
Location			
Anterior	8 (47.1%)	10 (25.6%)	0.182
Posterior	6 (35.3%)	24 (61.5%)	
Fundal	3 (17.6%)	5 (12.8%)	
Entering cavity	5 (29.4%)	12 (30.8%)	0.919

AUS = analgesic usage score; BMI = body mass index; CA125 = cancer antigen 125; SD = standard deviation; VNRS-6 = six-point verbal numeric rating scale.

approach because medical treatment is always transient and symptoms recur when medication is stopped.

The relationship between infertility and uterine adenomyoma is still uncertain, but severe endometriosis indeed impairs the successful pregnancy rate during assisted reproductive techniques [11]. To make the study population more consistent, we excluded patients with adenomyoma but coexistent adenomyosis or pelvic endometriosis and other pelvic diseases, or undergoing laparoscopic surgery, which has been mentioned before [28]. The main finding of our study was that the reproductive performance rate of women ($n = 56$) who underwent combined surgical–medical treatment for adenomyoma was as low as 41.1% (27 clinical pregnancies in 23 patients), which was lower than that in the study of Fedele et al (18 clinical pregnancies in 13 of a total 18 patients enrolled) [12]. In addition, the majority of pregnancies occurred within the first year after treatment (Table 2), suggesting that these women's ability to conceive was reduced by 25–33% each year after the completion of therapy. The definite reasons were unknown, but we supposed the following, including: (1) the relatively older age of this population (mean age, 38.3 years); and (2) only 60.7% of the 56 women had previously conceived, which is lower than the 90% of the general population or even lower than the cumulative pregnancy rate of 75.8% of the entire originally enrolled study population, suggesting the high possibility of subfertility in this subpopulation. However, the above reasons may be oversimplifications. Therefore, it was necessary to divide the 56 women into two groups: those that conceived successfully and those that did not, and look at the demographics and clinical characteristics of the patients.

In further looking for possible factors that affected future pregnancy, we divided the 56 women into two groups based on two endpoints: one ended with those that had a successful delivery and those that did not; and the other ended with those that conceived successfully and those that did not. Women who did not have a successful delivery were significantly older (40.6 ± 4.1 years vs. 32.1 ± 3.6 years, $p < 0.001$) and had significantly higher AUS (3.0 ± 1.3 vs. 2.0 ± 0.5, $p < 0.001$) than those who did. The regression model proved that age and baseline AUS were independent predictors of successful delivery during the 3-year follow-up (Table 4). In addition, this model accounted for 56.5% of the total variance related to future successful delivery. In further evaluating the role of age, it was interesting to find that all women, without an exception, who had a successful delivery, were older than 40 years.

One question brought to our attention in this study should be mentioned: we still failed to answer why the women's ability to conceive was reduced by 25–33% each year after the completion of therapy. In fact, all successful pregnancies following treatment with GnRH agonist for adenomyosis and/or adenomyoma and infertility occurred within 6 months, ranging from 1 to 6 months after discontinuation of medication [36–39]. This observation may be easily explained by the possibility of disease recurrence. By contrast, successful pregnancies after operative therapy for adenomyosis and/or adenomyoma can occur 30 months (ranging from 3 to 30 months) after complete surgery [2,27,40,41], suggesting that recurrence could be delayed by the surgical approach.

Therefore, in our study, was the reproductive performance in women with uterine adenomyoma after surgical–medical treatment due to disease recurrence or other variables, such as age or disease severity? We tried to answer this question. We divided the 23 women who had clinical pregnancies into two groups based on two endpoints: one ended with those that had a successful delivery at the end of the first year and those that did not; and the other ended with those that conceived successfully at the end of the first year and those that did not, and looked at the demographics and clinical characteristics of the patients (data not shown). It was interesting that the preoperative serum level of CA125 and the weight of the removed tumor were associated with successful delivery at the end of the first year, but none of above variables was correlated with successful spontaneous conception at the end of the first year.

Al Jama has reviewed 40 subfertile women with pathology-proved adenomyosis over a period of 8 years and found that higher baseline CA125 was significantly reduced postoperatively, along with the size of the uterus, suggesting that operative excision of the uterine adenomyoma could reduce the size of the uterus as well as the level of CA125 in patients with adenomyosis. However, this study did not look into the relationship between a low level of baseline CA125 and the future clinical pregnancy rate [42]. AI Jama also showed the benefits of surgical–medical therapy for future clinical pregnancy compared to medical treatment alone, because the 3-year cumulative clinical pregnancy rate of 44.4% (8/18) in patients who underwent surgical–medical treatment was

significantly higher than the 13.6% (3/22) in patients treated with GnRH agonist alone [42].

Another study has shown the high predictive values of CA125 to severity of disease, because high CA125 was correlated to a more severe disease status (revised American Society for Reproductive Medicine Classification Stage III and IV) [43]. Furthermore, Harada and colleagues have shown that a high level of CA125 in women with endometriosis seems to be related to concomitant adenomyosis [44]. Finally, a recent study from Patrelli and colleagues has shown that the serum CA125 level is significantly higher in patients with ovarian endometriosis and mixed endometriosis lesions than in those with extraovarian endometriosis lesions, and there is a significant correlation between CA125 and the surgical and pathological findings of ovarian and deep endometriosis [45].

These findings comply with the above-mentioned question: was the reproductive performance in women with uterine adenomyoma after surgical–medical treatment due to disease recurrence or other variables, such as age or disease severity, although the location did not affect the fertility rate [45]. In our study, we also showed that preoperative CA125 was not correlated with successful spontaneous conception (fertility rate) at the end of the first year. In addition, a stepwise multivariate linear regression analysis of the factors associated with successful delivery also excluded the value of preoperative CA125 level to predict future successful delivery.

We agree that surgical–medical therapy with conservative surgery should be considered as a more invasive and radical therapy for severely symptomatic women with adenomyoma, but our results seem to indicate clearly that age was the most important factor correlated with future successful delivery in these patients, suggesting that only highly selected patients might benefit from this approach.

The strength of this study is that it may be the study enrolling the largest population addressing the topic of surgical intervention for uterine adenomyoma, because we used the keywords “adenomyoma, surgery, uterine” to search for related published articles in PubMed and found no articles with a population as large as ours. We believe that this report might be useful as a reference for those women with uterine adenomyoma treated with surgical–medical therapy.

Some concerns should be mentioned. First, this study contained interoperator bias, because there were three doctors involved in this operation. The surgical technique might be difference among these doctors, and actually, it was also a fundamental discrepancy in all clinical studies involving the comparison of surgical outcome if the surgeries were performed by different doctors.

Second, these women might not have been homogeneous, because the fertility desire might have varied and some might have tried more aggressively than others to become pregnant, although we excluded those women who used contraception, searched for an assisted reproductive technique, or underwent laparoscopic surgery. We used stepwise multivariate linear regression analysis to detect the associations between successful delivery and demographics and clinical characteristics. All of these might have contributed to some differences in outcomes. For example, one study has suggested that the laparoscopic approach provides the best benefits in fertile patients with symptomatic leiomyoma, compared to the mini-laparotomy approach [46–49].

Third, this was a single-arm study without comparison and all women were treated with combination therapy; therefore, it was not clear whether surgery or medical treatment or combination therapy influenced the future successful pregnancy and/or delivery rates. Finally, there is still no agreement on the severity of uterine adenomyoma, and there is no single tool that can be used to predict this severity. Although we used many measures, including AUS, tumor size, serum CA125 level, and pain score (VNRS-6), none of them really reflected the patients’ situation. Analgesic use might be a reliable indicator of disease severity [50], because traditionally, medication use is often delayed until the patient cannot tolerate the pain [33]. That is why we found that only AUS, in addition to age, could predict the successful delivery rate.

In conclusion, younger age and lower baseline AUS are strong predictors for future successful delivery when women with uterine adenomyoma undergo combined surgical–medical treatment. The combination of conservative surgery and GnRH agonist treatment should be used with caution with older women who want to preserve their future fertility.

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