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Original Article

Fertility outcome of infertile women with adenomyosis treated with the combination of a conservative microsurgical technique and GnRH agonist: Long-term follow-up in a series of nine patients

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Abstract

Objective: This paper reports the long-term follow-up (62–83 months) of women with unexplained subfertility secondary to severe adenomyosis treated with the combination of conservative surgery and gonadotropin releasing hormone agonist (GnRH agonist) therapy.
Materials and Methods: A retrospective study included nine patients with a history of > 3 years of unexplained infertility who had extensive uterine adenomyosis. These nine couples were diagnosed with unexplained infertility after excluding other possible causes, such as the male factor, ovulation disorders, structural abnormality, and infections. All were essentially normal except for presumed uterine adenomyosis and elevated serum levels of CA125. All underwent a careful excision of the adenomyosis tissue using a microsurgical technique, and then a six-month course of GnRH agonist therapy. The outcome evaluations included serum level of CA125, degree of dysmenorrhea, and rate of spontaneous pregnancy.
Results: Postoperative follow-up showed that the severity of dysmenorrhea was significantly improved. The improvement scale was positively correlated with a decline in the serum level of CA125. A postoperative serum CA125 decreased to less than 10.00 IU/mL predicted well the spontaneous pregnancy rate, especially during the therapy. In the end, only two women became pregnant and finally delivered viable babies in this study.
Conclusions: Although the combination of careful conservative surgery and GnRH agonist therapy might provide some benefits in patients with unexplained infertility and presumed severe adenomyosis, two-thirds of the patients still failed to become pregnant. The postoperative serum level of CA125 could predict the future pregnancy rate.

Keywords: adenomyosis; CA125; cytoreductive and conservative surgery; gonadotropin releasing hormone agonist

Introduction

Uterine adenomyosis is a gynecologic condition whose diagnosis and clinical significance remains somewhat enigmatic [1,2]. An association between adenomyosis and infertility has not been fully established [3]. Some researchers believe that adenomyosis is not associated with subfertility,

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because it is widely held to be a condition associated with multiparity, and there have been several pathology-based studies published, in which women with adenomyosis found at hysterectomy were often more parous than women in whom it was not found [4,5]. By contrast, the possibility of an association between adenomyosis and subfertility has been raised in a few small case series in which fertility was restored after the successful treatment of adenomyosis with hormonal and/or surgical therapy [6–20]. The majority of patients were treated with gonadotropin-releasing hormone agonist (GnRH agonist) [6–11], and some were treated with surgery only [12,13]. However, the role of surgery in managing extensive uterine adenomyosis and subfertility is still highly controversial, partly because the diagnosis of adenomyosis has always been retrospective, and adenomyosis often involves the whole uterus diffusely, with difficulty separating normal myometrial tissue from myometrial tissue invaded by adenomyosis [16,18].

The surgical approach for preserving the uterus has become more popular, partly because some patients want to preserve their future fertility, and their dysmenorrhea does not respond to drug treatment [21]. For example, Fujishita et al used a transverse H incision technique to successfully treat extensive uterine adenomyosis [22]. In addition, a recent report from Morita et al also showed the possible benefits of using laparoscopic excision to manage well-defined adenomyoma, and concluded that this approach can provide a promising result [23], suggesting the possible benefits of the surgical approach to deal with extensive uterine adenomyosis.

We first attempted to use combination therapy, with medical and conservative surgical treatment, in managing subinfertile patients with extensive uterine adenomyosis [15]. In our previous reports, we highlighted the possible benefits of surgical attempt with/without GnRH agonist treatment for infertile women with severe dysmenorrhea and suspicious extensive uterine adenomyosis [16–18], and another report also supported this approach [19]. So far, long-term follow-up reports of this combination therapy have not been found in the literature. In order to clarify the role and/or effectiveness of this combination therapy for extensive uterine adenomyosis, this report evaluated the long-term fertility outcome of these subfertile women with unexplained infertility and presumed severe uterine adenomyosis, who were treated with microsurgical complete resection of the visible adenomyotic area followed by treatment with GnRH agonist.

Materials and methods

A total of nine women with a history of > 3 years of infertility were included in this study. The characteristics of all patients are summarized in Table 1. All nine patients were classified as having unexplained infertility, because no other possible causes of infertility were identified [24,25]. In addition, all these patients suffered from severe periodic colicky dysmenorrhea and occasional menorrhagia [26].

All patients underwent a microsurgical technique to avoid extensive injury to the uterus. This technique included an initial pitressin injection, a midline incision on the anterior wall, a meticulous coagulation, continuous irrigation with heparin-containing warm saline, careful excision of the adenomyotic tissue without damage to the uterine cavity, an adhesion prevention barrier (oxidized regenerated cellulose, ORC; Interceed; Johnson & Johnson Medical Inc., Arlington, TX), and a clearing of the abdominal cavity [27]. Among the nine women, one received a secondary operation two years later, after complete therapy using the same strategy owing to regrowth of the adenomyosis and exacerbation of dysmenorrhea, although she was treated with an intermittent course of GnRH agonist treatment during the follow-up (Table 2).

Results

All patients received a complete six-course of GnRH agonist therapy (3.6 mg goserelin acetate or 3.75 mg Leuprin depot) started immediately after operation (often within 48 hours). The follow-up duration ranged from 62 months to 83 months. All patients showed significant improvement in their symptoms or signs of dysmenorrhea or menorrhagia. For example, the severity of pain significantly decreased from a severe degree to a mild degree, or to an absence of pain, during the treatment. It was striking to find three patients (33%), who no longer complained of dysmenorrhea during the follow-up. Five of the remaining six patients had a re-attack of dysmenorrhea, but with less severity. Only one patient (No. 4) suffered from severe dysmenorrhea 30 months after the initial operation. This patient was treated with the same protocol again at the 32nd month after the initial operation, but only marginal improvement of her symptoms or signs was seen.

During the follow-up period, two-thirds of the patients ($n = 6$) received various cycles of assisted reproductive techniques (ART), but two of them became pregnant during the treatment. In the end, one-third of the women attained natural conception without the assistance of ART. Two of the 9 women delivered viable infants by a low transverse selective Cesarean section.

In a careful review of the women who became pregnant, we found that the postoperative serum levels of CA125 were always within the normal limit, and that all of them showed a serum level less than 15.00 IU/mL during therapy. In addition, the serum CA125 level of these patients was also maintained below 35.00 IU/mL.

Discussion

The term "adenomyosis uteri" was used first by Frankl [28]. Adenomyosis is defined as a benign invasion of the endometrium into the myometrium, producing a diffusely enlarged uterus, which microscopically exhibits ectopic, non-neoplastic endometrial glands and stroma surrounded by the hypertrophic and hyperplastic myometrium [29]. Most pathologists make a diagnosis of adenomyosis if the glandular extension below the endometrial myometrial interface (EMI) is greater than 2.5 mm [30]. Approximately 35% of adenomyotic cases are asymptomatic [29]. In the remaining cases, the symptoms start 1 week prior to the menstrual flow [14]. The most frequently

Table 1
The characteristics of the patients.

Characteristics	Patient								
	1	2	3	4[a]	5	6	7	8	9
Age (y)	33	34	31	35	37	37	34	35	32
Infertility[b]	1	2	1	1	2	1	1	1	1
Dysmenorrhea	S	S	S	S	S	S	S	S	S
Menorrhagia	Y	Y	N	Y	Y	Y	Y	Y	Y
Pelvic examination: All showed a firm and enlarged uterus									
Duration of infertility (years)	4	5	4	4	5	6	6	4	3
History of therapy	G	G	A	G, AIH	A	G, AIH, IVF	AIH, IVF	AIH	G, AIH, IVF
Preoperative evaluation									
Semen analysis[c]	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
Ovulation factor[d]	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
Tube/uterine factor[e]	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
Peritoneal factor[f]	WNL	E	WNL	WNL	WNL	WNL	WNL	E	WNL
Cervical factor[g]	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
Ultrasound size (cm)	13x	14x	11x	11x	14x	18x	13x	14x	11x
	14x	18x	12x	9x	13x	15x	14x	13x	11x
	15	12	9	12	14	16	11	13	10
Hormone[h]	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
CA125 (IU/mL)	106.9	164.5	89.1	115.3	196.4	145.5	69.5	292.4	143.5
Excision tissue (g)	240	420	120	105	280	190	195	345	90
Postoperative evaluation									
Postoperative follow-up (mo)	64	72	83	62	67	65	66	68	62
G therapy	P	P	P	P	P	P	P	P	P
Uterine size, 3M	9x	8x	8x	8x	8x	9x	8x	7x	7x
	8x	6x	8x	6x	7x	7x	5x	6x	7x
	9	5	7	8	8	6	7	6	6
Uterine size, 12 M	10x	8x	NA	9x	8x	12x	9x	7x	9x
	10x	9x		8x	6x	10x	8x	7x	7x
	7	6		9	5	8	6	5	6
CA125 (IU/mL) 3 M	14.8	15.5	12.2	15.6	9.6	12.1	17.2	7.8	13.4
CA125 (IU/ml) 12 M	67.6	49.6	NA	102.4	12.5	54.3	29.1	11.2	41.9
HSG 4 M	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
Spontaneous pregnancy	A	A	A	A	P	A	P	P	A
ART	A	P	P	A	P	P	P	P	A
Successful delivery of baby	A	A	A	A	P	A	A	P	A

A = absence; AIH = artificial insemination from her husband; ART = assisted reproductive techniques, including AIH or IVF; E = extra-uterine endometriosis; G = GnRH agonist treatment; HSG = hysterosalpingography; IVF = in-vitro fertilization and embryo transplantation; M = months; NA = no data available; P = presence; S = severe; WNL = within the normal limits.

[a] This patient underwent cytoreductive surgery twice.

[b] 1 refers to primary infertility and 2 refers to secondary infertility.

[c] The evaluation of male factor infertility was based on the normal values suggested by the world Health Organization (WHO), including volume < 2.0 mL; sperm concentration < 20 million/mL; motility < 50%; morphology < 30% normal forms.

[d] Documentation of ovulation included basal body temperature, midluteal serum progesterone, LH surge, ultrasound monitoring, and endometrial biopsy.

[e] Based on hysterosalpingography, a normal contour of the uterine cavity and patency of bilateral tubes were found.

[f] Based on laparoscopic examination, no paratubal adhesion, no extrauterine endometriosis and only an enlarged, firm uterus were found.

[g] Normal cervical mucus–sperm interaction.

[h] Hormone survey included serum prolatin level, thyroid-stimulating hormone, FSH, DHEAS, DHEA and testosterone level.

cited profile comprises the triad of abnormal uterine bleeding (50%), secondary dysmenorrhea (30%), and an enlarged, tender uterus [3]. The dysmenorrhea pattern often presents as cramps and colic pain, with a heavy amount of blood during menstruation, and also nightmares for these patients. In addition to dysmenorrhea, more than two-thirds of the patients in this study also suffered from menorrhagia. Adenomyosis of the uterus is often described as scattered, widely distributed endometrial glands or stromal tissue throughout the myometrium layer of the uterus. Sometimes, adenomyosis can form a mass lesion within the myometrium, often called an adenomyoma [18,31].

The relation between infertility and uterine adenomyosis is still uncertain, but severe endometriosis indeed impairs the successful pregnancy rate during the artificial ART. To date, there is no uniform agreement on the most appropriate therapeutic methods for managing the uterine adenomyosis [16–18], partly because the diagnosis of adenomyosis has always been retrospective, and only a surgical approach can identify it correctly. Recent reports highly recommend that high-resolution magnetic resonance imaging and/or ultrasound may offer a relatively more accurate predicted value in the diagnosis or localization of adenomyosis and/or adenomyoma [32,33].

Table 2
Summary of nine patients with adenomyosis treated with conservative surgery and GnRH agonist.

	Baseline (M ± SD)	3 months (M ± SD)	12 months (M ± SD)	$p1$[a]	$p2$[a]	Remarks
UT volume	1196 ± 543	194 ± 68	264 ± 130	0.0006	0.0006	
CA125	147.0 ± 67.0	13.1 ± 3.0	46.1 ± 30.2	0.0004	0.0009	
Pain score	4.7 ± 0.5	0.33 ± 0.5	1 ± 0.9	0.000	0.000	
Satisfaction	1 ± 0	3 ± 0	2.8 ± 0.4	0.000	0.000	
Spontaneous pregnancy						3/9, 33.3%
ART						6/9, 66.7%
Successful delivery						2/9, 22.2%

ART = assisted reproductive techniques; M = mean; $p1$ = difference between baseline and 3 months; $p2$ = difference between baseline and 12 months; SD = standard deviation; UT = uterine.
[a] Student t test was used for analyzing the difference between the two groups.

GnRH agonist is the most commonly used therapy, yielding a reduced myoma size [34–36] and possibly suppressing endometriosis [37–39]. This strategy has resulted in a few case reports of successful pregnancy and delivery, but its effect is often transient, and is often used with a preoperative adjuvant therapy. Surgical intervention is seldom considered to play a role in managing such patients. The most important consideration is the difficulty of selecting a good candidate to undergo this surgical approach; because, how do you determine the extent of adenomyosis in a particular patient? Furthermore, adenomyosis is not cleared completely by conservative surgery. In addition, postoperative sequels, such as pelvic adhesion, cannot be completely avoided [40]. Finally, the rupture of a pregnant uterus has been observed after myomectomy [41–44]. In this study, the age of the all patients was $>$ 30 years, and the duration of infertility was more than 36 months; as such, these were not good candidates to receive expectant management [3,4]. Menorrhagia is also a symptom presenting, and this constitutes a definite indication for operation [5]. The patients in this study also suffered from increasing dysmenorrhea, which subsequently impaired them from performing their daily work, due to a huge and firm uterus. In the end, the probability of a spontaneous pregnancy was not great, even though GnRH agonist was used to treat these patients. Two patients underwent a variable course of GnRH agonist treatment, but to no effect. Considering all the above-mentioned reasons, there seemed to be a strong rationale supporting the use of surgery.

The beneficial role of the combination of cytoreductive surgery and GnRH agonist treatment in managing infertile women with adenomyosis could include the removal of a tumor with a relatively poor blood supply, and the enhancement of the immune function of the host, which can result in enhancing the response of the remaining tumor to chemotherapy. In addition, the huge size of uterine myoma and uneven distribution of medication could explain why the variability in the response among individuals treated with GnRH agonist to reductions of uterine myoma volume is so great. The serum marker CA125 is useful for long-term screening and/or monitoring of endometriosis [45]. Yen et al also suggested that the CA125 level may be a valuable indicator for monitoring the efficacy of laparoscopic bipolar coagulation of the uterine vessels for symptomatic myomas in women with elevated CA125 [46]. In this study, we also found that the serum CA125 level is a good indicator for monitoring the efficacy of the combination of conservative surgery and GnRH agonist therapy for symptomatic adenomyosis in women with subfertility. In agreement with the above finding, the severity of dysmenorrhea is also negatively correlated with the serum CA125 level, suggesting that part, if not all, of tumor (adenomyosis) behavior may also involve the disease progression during therapy; however, we cannot provide evidence to support this hypothesis.

In conclusion, this report further supports the concept that the combination of microsurgical cytoreduction and GnRH agonist treatment could be appropriate in patients who have failed GnRH agonist treatment alone or who do not have tolerance of long-term GnRH agonist treatment, with presumed severe adenomyosis, such as a huge and firm uterus, severe dysmenorrhagia, and clinically unexplained subfertility. The postoperative serum level of CA125, either three months or 12 months later, could predict the outcome of these patients, including the restoration of fertility and improvement of dysmenorrhea. Since two-thirds of the patients did not become pregnant, and some patients had recurrent dysmenorrhea, we do not think this strategy should be routine in managing woman with presumed adenomyosis, partly because the diagnosis of adenomyosis has always been retrospective, partly because the use of GnRH agonist can be effective, and partly because of the long-term effect (more than 10 years) is unknown.

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