Effectiveness of Postoperative Adjuvant Therapy in Improving Reproductive Outcome of Endometriosis-associated Infertility

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Background and purpose: Treatment of endometriosis-associated infertility has not yet become standardized. Various protocols including surgical treatment, medical therapy, and a combination of both have been suggested but their use remains controversial. The objective of the present study was to determine whether postoperative adjuvant therapy for endometriosis is effective in improving reproductive outcome.

Methods: Medical records of infertile patients with newly diagnosed endometriosis treated in a university teaching hospital during a 50-month period were reviewed. After exclusion of patients with other major infertility factors, a total of 209 patients were included in the retrospective analysis. These patients were divided into those receiving (n = 78) or not receiving (n = 131) peri- or postoperative adjuvant medical therapy. The adjuvant therapies included danazol (n = 62), gonadotropin releasing hormone analogues (n = 11), progestins (n = 3), oral contraceptives (n = 1), and mixed treatment (n = 1).

Results: The pregnancy rate was lower in those receiving adjuvant therapy, although this result was not significant (32.1% *vs* 45.8%; $p = 0.05$). When patients using postoperative danazol therapy were considered alone, the pregnancy rate in patients receiving adjuvant therapy was significantly lower than that in patients not receiving it ($p = 0.047$). When the stage of endometriosis was considered, the pregnancy rate in patients receiving adjuvant therapy was again lower than in those not receiving it in patients with minimal or mild endometriosis (42.9% *vs* 60%; $p = 0.043$). However, in patients with moderate or severe endometriosis, the pregnancy rate was not different in the two groups (31% *vs* 36%; $p = 0.56$). Postoperative assisted reproductive techniques (ART) including controlled ovarian hyperstimulation/intrauterine insemination (COH/IUI) and *in vitro* fertilization (IVF) were effective in improving the pregnancy rates for all patients (53.9% with ART *vs* 33.1% without; $p = 0.003$) and for patients with advanced endometriosis (47.7% with ART *vs* 27.2% without; $p = 0.016$).

Conclusions: Our results suggest that postoperative adjuvant therapy is ineffective in improving reproductive outcome in patients with either early (minimal or mild) or advanced (moderate and severe) endometriosis. This finding suggests that if fertility is the goal of treatment, adjuvant therapy may be unnecessary after surgery. In contrast, our data suggest that empirical ART, including COH/IUI or IVF, may be a better alternative to improve the pregnancy outcome after surgery.

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Endometriosis is a common disease among women in their reproductive years, and is especially prevalent among women with infertility problems. The relationship between endometriosis and infertility is enigmatic, though it is generally agreed that endometriosis plays a critical role in infertility [1–4]. Endometriosis and its

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associated infertility have a multifactorial etiology, which includes dysfunction and mechanical disruption of ovulation, altered folliculogenesis, sperm phagocytosis, impaired fertilization and implantation, distortion of pelvic anatomy, inefficient gamete transfer, luteal phase deficiency, inhibition of early embryo development, immunologic alteration, and changes in peritoneal fluid [1, 5–9]. The best treatment for endometriosis-associated infertility remains controversial [5, 6, 10]. However, the available modalities include medical therapy with a number of hormone preparations designed to suppress the disease, surgical treatment designed to debulk the disease and repair anatomic distortion, or a combination of both [3].

Several medications including oral contraceptives, danazol, progestins, gonadotropin releasing hormone analogues (GnRH-a), and antiprogestins are very useful in pain relief. However, it has been found that pelvic adhesion, endometrioma, and fibrous sequelae in moderate or severe endometriosis respond less favorably to medical treatment. In addition, infertile patients with minimal or mild endometriosis fail to benefit from medical treatment [11, 12]. It is therefore generally agreed that ovulation suppression alone serves little benefit and cannot be recommended as a primary approach in treating endometriosis-associated infertility [1, 6, 13]. On the contrary, surgical intervention usually provides better prognosis for these patients. Conventional laparotomy or operative laparoscopy to treat endometriotic lesions and reconstruct the pelvic anatomy are reasonably effective in relieving infertility caused by endometriosis [5, 6, 14].

However, the role of adjuvant therapy after surgery is not established [15, 16], as most previous studies have found it ineffective [5]. Combined medical and surgical treatments for endometriosis-associated infertility have been considered inappropriate due to findings that medical treatment did not improve pregnancy rates and delayed the time to conception [5, 6]. In addition, superfluous treatment cost and undesirable side-effects may occur with the use of medication [17].

Many physicians in Taiwan remain accustomed to providing postoperative adjuvant therapy because they consider it to improve reproductive outcome. The present study sought to determine whether postoperative adjuvant therapy is effective in improving fecundity.

Materials and Methods

We reviewed the medical records of 1,095 patients with surgically confirmed endometriosis. Patients who were less than 40 years old, treated at National Taiwan University Hospital between August 1995 and October 1999, and with newly diagnosed endometriosis and associated infertility, exclusive of other major fertility problems such as ovulatory, uterine, cervical or male factors, were included in the analysis. Subjects lost to follow-up after treatment were excluded.

The final study group comprised 209 patients. Endometriosis was diagnosed either by laparoscopy or laparotomy. The severity of the disease was scored and staged according to the revised American Fertility Society (rAFS) classification [18]. Data on age, reproductive history, duration of infertility, serum CA125 concentrations, stage of endometriosis, method of surgical management, modality of medical adjuvant treatment, fertility enhancement strategy, and pregnancy outcome were collected from medical records. Patients were divided into those receiving (n = 78) and those not receiving (n = 131) peri- or postoperative adjuvant therapy. All patients were observed until April 2000, with follow-up periods ranging from 6 months to 5 years. For patients who became pregnant, the follow-up period was extended until the pregnancy outcome was available.

The results were analyzed using Student's *t*-test, Fisher's exact test, or chi-square test where appropriate. A p value of less than 0.05 was considered statistically significant.

Results

The age of patients ranged from 20 to 39 years (mean ± SD, 31.6 ± 3.7 yr). Primary infertility was the reason for treatment in 52.6% (110) of patients and the duration of infertility ranged from 1 to 14 years (2.6 ± 2.7 yr). Serum CA125 concentration (90.0 ± 131.1 IU/mL; range, 4.0–946.4) and rAFS score (37.4 ± 35.1; range, 3–148) ranged widely. The mean age (31.0 ± 3.6 *vs* 31.9 ± 3.7 yr), gestational number (0.6 ± 1.0 *vs* 0.9 ± 1.2), duration of infertility (2.1 ± 2.3 *vs* 2.8 ± 2.9 years), and serum CA125 concentrations (101.5 ± 95.2 IU/mL *vs* 79.9 ± 156.5 IU/mL) were not significantly different between the adjuvant therapy and non-adjuvant therapy groups. Although the rAFS scores were significantly different (49.2 ± 34.7 *vs* 30.4 ± 33.6; $p < 0.01$), this disparity was not found when patients were further categorized into early (stage I or II rAFS classification; n = 62) and advanced (stage III or IV; n = 147) endometriosis groups. That is, both in early and advanced endometriosis the rAFS scores were not different between those receiving peri- or postoperative adjuvant therapy or not (Table 1).

Most patients with early disease underwent laparoscopic diagnosis and treatment (55/62), but a

Table 1. Clinical characteristics of patients with endometriosis-associated infertility

	Adjuvant therapy	No adjuvant therapy	*p* value
n	78	131	
Age (yr)	31.0 ± 3.6	31.9 ± 3.7	0.101
Gestational number	0.6 ± 1.0	0.9 ± 1.2	0.185
Duration of infertility (yr)	2.1 ± 2.3	2.8 ± 2.9	0.055
Serum CA125 (IU/mL)	101.5 ± 95.2	79.9 ± 156.5	0.467
Revised AFS score	49.2 ± 34.7	30.4 ± 33.6	< 0.001
Early endometriosis	5.6 ± 3.9	4.8 ± 2.8	0.613
Advanced endometriosis	53.5 ± 33.4	49.0 ± 33.4	0.409

AFS = American Fertility Society.

significant portion of patients with advanced disease were treated via laparotomy (58/147) (Table 2). The medical adjuvant therapies used in this study included danazol (n = 62; duration of application, 4.35 ± 1.84 mo), GnRH-a (n = 11; 5.0 ± 1.61 mo), progestins (n = 3; 4.33 ± 1.52 mo), oral contraceptives (n = 1; 7 mo), or mixed treatment (n = 1; 4 mo). Most adjuvant therapies were used after surgery (n = 72).

During the follow-up period, pregnancy was achieved in 85 patients (cumulative pregnancy rate, 40.7%). Among these, 68 pregnancies were full term, four were preterm, one was extrauterine, and 12 ended in miscarriage.

When all patients were considered together, the pregnancy rate showed a trend towards a lower success rate in those receiving adjuvant therapy as opposed to those not receiving it, although this difference was not significant (32.1% *vs* 45.8%; $p = 0.05$). However, this trend became significant when the subgroup of patients receiving danazol was analyzed separately. In the danazol group, the pregnancy rate in patients receiving adjuvant therapy (19/62) was significantly lower than in those not receiving adjuvant therapy (66/147; $p = 0.047$). Due to the fact that physicians tended to use postoperative adjuvant therapy in more severe cases, we further analyzed the effectiveness of adjuvant therapy in different stages of endometriosis, and found that among patients with early endometriosis (stage I and II), the pregnancy rate in those receiving adjuvant therapy was again lower than in patients not receiving it (42.9% *vs* 60.0%; $p = 0.043$). However, in patients with advanced endometriosis (stage III and IV), the pregnancy rate was not significantly different in the two groups (32.1% *vs* 35.5%; $p = 0.56$) (Table 3).

Postoperative ART including controlled ovarian hyperstimulation/intrauterine insemination (COH/IUI) and *in vitro* fertilization (IVF) was used in 76 patients (36.4%) in the present study. During the first 6 months, next 6 months, next 1 year, and after 2 years, there were 36, 31, 11, and 0 patients who received COH/IUI and 11, 13, 19, and four patients who received IVF, respectively. Postoperative ART was effective in improving the pregnancy rate for all patients (53.9% with ART *vs* 33.1% without; $p = 0.003$) including patients with advanced disease (47.7% with ART *vs* 27.2% without; $p = 0.016$). However, patients with early endometriosis showed no significant differences or trends in pregnancy rate (62.5% with ART *vs* 53.3% without; $p = 0.465$) (Table 4). In contrast, ovulation induction with clomiphene and/or gonadotropins alone did not exert a significant effect on the pregnancy rate (data not shown).

Table 2. Surgical methods and main procedures used in the treatment of early and advanced endometriosis

	Early*	Advanced†	Total
Laparoscopy	55	88	143
Diagnosis only	19	18	37
Electrocauterization	26	5	31
Adhesiolysis	10	3	13
Enucleation		58	58
Oophorectomy		4	4
Laparotomy	7	58	65
Diagnosis only	3	0	3
Electrocauterization	1	1	2
Adhesiolysis	1	2	3
Enucleation	1	45	46
Oophorectomy	1	10	11
Scope shift to laparotomy		1	1
Total	62	147	209

*Stage I or II endometriosis according to the revised American Fertility Society (AFS) classification; †stage III or IV endometriosis according to the revised AFS classification.

Discussion

In the present study, adjuvant therapy did not further improve reproductive outcome after surgical treat-

Table 3. Reproductive outcome in patients with different severity of endometriosis

	Adjuvant therapy	No adjuvant therapy	*p*-value
Early	3/7	33/55	0.043
Advanced	22/71	27/76	0.56
Total	25/78	60/131	0.05

Number of cases with pregnancy/total number of cases = pregnancy rate.

Table 4. Reproductive outcomes in patients with early and advanced endometriosis according to the use of assisted reproductive techniques (ART)

	Without ART	With ART	*p*-value
Early	16/30	20/32	0.465
Advanced	28/103	21/44	0.016
Total	44/133 (33.1%)	41/76 (53.9%)	0.003

Number of cases with pregnancy/total number of cases = pregnancy rate.

ment for endometriosis. This result held even when patients were sub-grouped into early and advanced disease groups, in order to prevent bias due to the severity-dependent choice of postoperative adjuvant therapy. These data suggest that postoperative adjuvant therapy has a negative effect on conception in patients with early endometriosis, possibly due to delay in attempting conception.

Although danazol has repeatedly been shown to exert beneficial effects on the extent of endometriosis and its related symptoms, there have been few reports supporting its use in the treatment of endometriosis-associated infertility [1, 19]. Similarly, the roles of medical treatment with antiprogestins or GnRH-a for endometriosis-associated infertility remain unclear [5, 6, 20].

However, many physicians in Taiwan remain accustomed to providing postoperative adjuvant therapy because they consider that it improves reproductive outcome. The present study provides further evidence against the use of postoperative adjuvant therapy with danazol in treating endometriosis-associated infertility. This conclusion may also be applicable to GnRH-a, though a definite conclusion could not be reached due to the small number of cases.

The findings of this study demonstrate that if fertility is the goal of treating endometriosis, postoperative adjuvant therapy is unnecessary and may be counterproductive. This is probably especially true in patients with an expected short residual reproductive period (older patients or patients with poor ovarian reserve).

However, the use of short courses of GnRH-a after surgery will probably be useful when IVF is scheduled to follow very soon after surgery. Using this protocol, GnRH-a may be regarded as an agent for ovulation induction. In addition, the present study did not completely exclude a role for postoperative adjuvant therapy because the endometriosis recurrence rate was not evaluated. In advanced endometriosis, pelvic reconstruction is sometimes difficult to perform and postoperative adhesion is also a common sequela affecting ensuing pregnancy. In view of the fact that less than 50% of patients in this study actually achieved pregnancy during the follow-up period, the role of adjuvant therapy in alleviating or reducing disease recurrence must be also considered. For those patients who do not achieve pregnancy in due course, recurrence may be an important determinant of fecundity. It is reasonable to speculate that postoperative adjuvant therapy may be useful if its use could further lengthen the time to recurrence of endometriosis. Nevertheless, the advantage of medical treatment after laparoscopic treatment for the prevention of recurrence in advanced endometriosis has not been demonstrated [15]. The time to recurrence of endometriosis-associated pain after either danazol or GnRH-a treatment is unsatisfactorily short [21]. In contrast, the rate of recurrence after surgery is not as high as was previously thought and appears to be correlated with the duration of follow-up [22]. Further analysis of recurrence data with a longer follow-up may help clarify the role of postoperative adjuvant therapy. Consideration of these results may allow the development of a more comprehensive treatment protocol.

The exact role of ART in endometriosis-associated infertility has also been controversial. COH/IUI was shown to shorten the period to pregnancy without changing the overall fertility [11]. However, several studies have demonstrated that the use of superovulation with IUI and IVF is effective in overcoming endometriosis-associated infertility [6, 23–26]. Generally, ART is most beneficial for those who have failed other treatments, are late in their reproductive age, have prolonged duration of infertility, or multiple factor infertility [6]. Interestingly, IVF has been recommended as the first-line treatment for minimal endometriosis-associated infertility [27]. The present study thus provides further evidence to support the role of ART and clearly indicates that ART including COH/IUI and IVF is effective in improving the pregnancy rate after surgery.

Finally, in the interpretation of the present results, several issues need to be considered. First, our results were obtained from a retrospective study in a selected population, which inevitably has its own unique characteristics. The lack of large-scale prospective randomized controlled trials leaves the results open to question. Secondly, since the effectiveness of a specific operation depends significantly on the skill and experience of the surgeon, the use of data from multiple operators in this study may also have confounded the analysis.

In conclusion, the present study suggests that if fertility is the primary goal, postoperative adjuvant therapy is unnecessary for the treatment of endometriosis. Our results also suggest that empirical ART, including COH/IUI or IVF, may be a better alternative for this goal.

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