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Review

Management of the Pain Associated with Endometriosis: An Update of the Painful Problems

Yuka Ozawa, Takashi Murakami, Yukihiro Terada, Nobuo Yaegashi, Kunihiro Okamura, Shinichi Kuriyama[1] and Ichiro Tsuji[1]

Department of Obstetrics and Gynecology, and
[1]Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan

Ozawa, Y., Murakami, T., Terada, Y., Yaegashi, N., Okamura, K., Kuriyama, S. and Tsuji, I. *Management of the Pain Associated with Endometriosis: An Update of the Painful Problems*. Tohoku J. Exp. Med., 2006, **210** (3), 175-188 —— Endometriosis is a condition characterized by ectopic endometrial tissues located outside of the uterus, most commonly found on the pelvic peritoneum or ovary. Endometriosis, which occurs in 7-10% of women in the general population and 71-87% of women with chronic pelvic pain, is associated with dysmenorrhea, chronic pelvic pain, and infertility. There is considerable debate about the effectiveness of various interventions for endometriosis. This review discusses the benefits and drawbacks of pharmacologic and surgical treatments for the pain associated with endometriosis. Laparoscopic surgery has been demonstrated to relieve the pain associated with endometriosis. Hormonal therapies, such as gonadotropin-releasing hormone (GnRH) analogues or the weak androgen danazol, have also been effective at relieving the pain associated with endometriosis. Oral contraceptives appear to be as effective as GnRH analogues for pain relief. Although both surgical and pharmacologic treatments have been effective for relief of the pain associated with endometriosis, the recurrence rate remains significant. The management of pain associated with endometriosis has thus not been satisfied. Larger unified clinical trials are needed to evaluate the effectiveness of new treatments in managing the pain associated with endometriosis. ———— endometriosis; pain management; meta-analysis

Endometriosis is the presence of ectopic endometrial tissues outside of the uterus, found most commonly on the pelvic peritoneum or ovary. Endometriosis occurs in 7-10% of women in the general population, including as many as 50% of premenopausal women (ACOG practice bulletin 2000), 38% (2-50%) of infertile women, and 71-87% of women with chronic pelvic pain. Endometriosis is associated with dysmenorrhea, chronic pelvic pain, and infertility. Laparoscopy is the most important diagnostic tool for endometriosis. Extent of the disease is based on the revised scoring system of the American Fertility Society (R-AFS), established in 1985, with minimal, mild, moderate, and severe stages.

Endometriosis is a common cause of mor-

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Correspondence: Yuka Ozawa, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai, Japan.
e-mail: ozawa@mail.tains.tohoku.ac.jp

bidity in reproductive age females. For this population, conservative surgery that does not permanently harm the reproductive organs is necessary. Laparoscopic surgery is the standard for treatment of child-bearing women with endometriosis as current pharmacological therapies interrupt normal cyclic ovarian hormone production, resulting in an environment that is not conducive to the growth of endometriosis, but also not permissive for child bearing. Currently accepted medical therapies for endometriosis include the weak androgen danazol, gonadotropin-releasing hormone (GnRH) analogues, and oral contraceptives (OC).

Significant debate surrounds the effectiveness of various interventions for endometriosis. Meta-analyses or systematic reviews can resolve such confusion; such meta-analyses exploring the management of infertility associated with endometriosis have previously been published (Adamson and Pasta 1994; Hughes et al. 1997).

This review discusses the benefits and drawbacks of pharmacologic and surgical treatments for the pain associated with endometriosis.

Materials and Methods

Search strategy for the identification of studies

We performed a systematic search of MEDLINE from 1964 to July 2006. The database used the relevant medical subject heading search (MeSH) with the term "endometriosis". Selected sub-headings were human, female, English, randomized controlled trial (RCT), and clinical trial (CT). We searched reference lists of review articles from January 1964 to July 2006. We also identified published RCTs, CTs, case-control studies, cohort studies, and descriptive studies.

Criteria for considering studies for this review

Inclusion criteria.

A. Type of intervention
pharmacologic and/or surgical therapy
pharmacologic: OC, GnRH analogues, and danazol.

B. Measures of outcomes
improvement of pain

C. Types of studies
RCT, CT, cohort, case-control, descriptive

Exclusion criteria.

A. Type of intervention
pharmacologic treatment: add-back therapy
surgical treatment: hysterectomy and/or bilateral oophorectomy

Meta-analysis design

We conducted meta-analysis when the results differed between studies. The homogeneity of the estimators of the odds ratio (OR) was tested using the 'large sample test', which was based on the Q statistics. The fixed-effect model (Mantel-Haenszel method) was used to calculate the summary OR and the 95% confidence interval (95% CI).

Results

A. Surgical management

Two RCT studies (Sutton et al. 1994; Abbott et al. 2004) and two cohort studies (Sutton et al. 1997; Jones et al. 2001) of laparoscopic surgery were eligible for our review (Table 1).

One double-blinded RCT (Sutton et al. 1994) and two cohort studies compared laser ablation plus uterine nerve ablation to diagnostic laparoscopy alone for relief of the pain associated with minimal to moderate endometriosis. Three months after surgery, there were no significant differences in pain relief; 56% of patients in the laser group experienced pain relief in comparison to 48% in the control group. At six months, however, there was a significant difference in pain relief (62.5% vs 22.6%) that continued at the one-year follow-up in 90% of those in the treatment group who initially responded.

The cohort studies performed a long-term follow-up of patients who received therapeutic laparoscopic surgery, including patients with as much as six months of expectant management therapy in a previous RCT. The mean follow-up time after surgery was 73 months. Painful symptoms recurred in 73.7% of patients, with a median time of recurrence of 19.7 months (range: 5-60). At follow-up, satisfactory symptom relief was reported in only 55.3% of the patients. The remaining 44.7% of patients continued to experience pain; eight eventually required hysterectomy.

Abbott et al. (2004) examined the effect of full laparoscopic excision of endometriosis

TABLE 1. Comparing of laparoscopic treatment and expectant management for treatment of the pain associated with endometriosis.

Authors (Year)	Type of study	Therapy group (Subjects)	Control group (Subjects)	Measurement parameter	Results	Statistics
Abbott et al. (2004)	RCT	20	19	Symptom relief rate	80% vs 32% (Therapy vs Control group)	sig.
				EQ-5D VAS	83.6 ± 10.8 vs 65.9 ± 21.3	sig.
Sutton et al. (1994)	RCT	32	31	Symptom relief rate	62.5% vs 22.6%	sig.
Sutton et al. (1997)	Cohort*	38		Recurrence rate	73.7%	
				Time to recurrence	19.7 months	
Jones et al. (2001)	Cohort*					

Laparoscopic surgery relieves the pain associated with endometriosis.

EQ-5D VAS is a self-rated measure of a patient's health status using a weighted utility index based on five components of health – mobility, self-care, usual activities, pain, and anxiety or depression.

sig., significant. *similar study designs.

lesions with placebo surgery on pain and quality of life for women with all stages of endometriosis. Six months after surgery, a greater number of women in the excisional surgery group (80%) reported an improvement in their symptoms in comparison with women in the placebo surgery group (32%). Other aspects of quality of life score were also significantly improved six months after excisional surgery, but not after the placebo procedure.

In summary, laparoscopic surgery, including laparoscopic uterine nerve ablation, appears to be an effective method to relieve the pain associated with endometriosis.

B. Pharmacologic management

1) OC

We could not identify any epidemiological studies of OC that satisfied the eligibility criteria.

In the late fifties, descriptive studies (Kistner 1958, 1959) suggested that induction of pseudopregancy was effective. Seven of 10 patients who received estrogen plus progesterone for three months exhibited relief of dysmenorrhea and dyspareunia. In addition, four of five patients who received estrogen plus progesterone for four to six months, and three of four patients who received estrogen plus progesterone for seven to 10 months also demonstrated relief of these symptoms.

2) GnRH analogues

Of the five RCT studies (Dlugi et al. 1990; Miller 1990; Fedele et al. 1993; Bergqvist et al. 1998; Ling 1999) on GnRH analogues eligible for this review (Table 2), one examined treatment of clinically suspected endometriosis (Ling 1999). The others explored minimal to mild endometriosis (Fedele et al. 1993), minimal to severe endometriosis (Dlugi et al. 1990; Bergqvist et al. 1998), or unclassified endometriosis (Miller 1990).

An RCT that compared GnRH analogues with placebo for the treatment of clinically suspected endometriosis demonstrated that three months of therapy with GnRH analogues significantly reduced post-treatment dysmenorrhea, pelvic pain, dyspareunia, and pelvic induration and tenderness (Ling 1999).

Fedele et al. (1993) compared a six-month administration of GnRH analogues with expectant management of minimal to mild endometriosis. GnRH analogues significantly improved the pain symptoms that continued to persist in approximately half of patients 18 months after the end of treatment. Symptoms associated with endometriosis, however, spontaneously disappeared in approximately one fifth of untreated patients.

Six-month administration of GnRH analogues was compared with placebo as treatment

TABLE 2. Comparing of GnRH analogue administration with placebo for treatment of the pain associated with endometriosis.

Authors (Year)	Type of study	Therapy group (Subjects)	Control group (Subjects)	Measurement parameter	Results (Therapy vs Control group)	Statistics
Ling (1999)	RCT	50	50	Post-therapy change in the 10-point pain scale value	–7.4 vs –1.6	sig.
Fedele et al. (1993)	RCT	19	16	Dysmenorrhea rate at three months Dysmenorrhea rate at 12 months	27% vs 81% 47.5% vs 81%	sig. sig.
Bergqvist et al. (1998)	RCT	24	25	Post-therapy change in the three-point pain scale value	–2.85 vs –0.33	sig.
Dlugi et al. (1990)	RCT	32	31	Change in the three-point pain scale value one year after treatment	–2.2 vs –0.2	sig.
Miller et al. (1990)	RCT	28	20	Symptom relief rate	Not described	sig.

GnRH analogues were demonstrated to relieve the pain associated with endometriosis.

Ten-point pain scale is a linear scale on which 0 indicates the absence of pain and 10 represents severe pain. The three-point pain scale is a linear scale on which 0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain.

for minimal to severe (Dlugi et al. 1990; Bergqvist et al. 1998) or unclassified endometriosis (Miller 1990). While GnRH analogues significantly reduced pain, the effects of GnRH analogues on dyspareunia were not consistent.

In summary, GnRH analogues relieve the pain associated with endometriosis. No studies, however, have followed patients beyond 12 months.

3) Danazol

Two RCT studies (Telimaa et al. 1987; Kauppila et al. 1989) on danazol, eligible for review, utilized similar trial designs (Table 3).

These RCT studies compared six-month administration of danazol or medroxyprogesterone acetate (MPA) with placebo. Both danazol and MPA significantly reduced post-treatment pain and symptoms. Six months after completing therapy, symptom scores were reduced by 63% and 54% in the danazol and MPA groups, respectively, whereas scores increased by 48% in the placebo group. Danazol, however, caused more androgenic and metabolic side effects than placebo.

Danazol therapy also relieves the pain associated with endometriosis. No studies, however, have followed patients beyond 12 months of

TABLE 3. Comparing of danazol and placebo for management of the pain associated with endometriosis.

Authors (Year)	Type of study	Therapy group (Subjects)	Control group (Subjects)	Measurement parameter	Results (Therapy vs Control group)	Statistics
Kauppila et al. (1989)	RCT*	20	19	Change in the three-point pain scale	–63% vs +48%	sig.
Telimaa et al. (1987)	RCT*					

Danazol therapy was shown to relieve the pain associated with endometriosis.

sig., significant. *similar study designs.

treatment.

4) OC and GnRH analogues

One RCT study (Vercellini et al. 1993) on OC and GnRH analogues (Table 4) compared OC administration for six consecutive months with six-month treatment with GnRH analogues. After the six-month treatment period, the prevalence of dysmenorrhea in the two groups could not be compared, because almost all of the patients in the GnRH analogue group became amenorrheic. The reduction in pain score was significant in both groups. There were no differences between the groups in the reduction of dyspareunia or non-menstrual pain. Furthermore, there were no differences in the recurrence of symptoms six months after treatment completion. Of the side effects, patients were more likely to experience hot flashes and vaginal dryness while taking the GnRH analogues than while receiving OC.

In summary, OC were as effective as GnRH analogues for the relief of symptoms associated with endometriosis. Only one study comparing these treatments, however, could be identified.

5) OC and danazol

We could not identify any epidemiological studies that compared the effects of low-dose OC and danazol. In the 1970s, two RCTs (Noble and Letchworth 1977, 1979) compared pseudopregnancy treatment (six-month treatment with Enavid: 75 μg mestranol and l5 mg norethynodrel/day) with a six-month danazol treatment.

In one of these studies (Noble et al. 1977), only two of the five patients in the low-dose OC group completed six months of treatment, neither of which exhibited any improvement in symptoms. Of the nine of 11 patients in the danazol group who completed the six-month treatment, all demonstrated an improvement in physical symptoms. In addition, danazol was less likely to cause side effects.

In the second RCT (Noble and Letchworth 1979), 41% of the Enavid group and 4% of the danazol group could not complete more than five months of treatment because of side effects. Cure rates were 30% and 62% with improvement rates of 0% and 25% in the Enavid and danazol groups, respectively. The side effects of the OC treatment were potentially serious, indicating that danazol is superior to pseudopregnancy as therapy for endometriosis.

These trials, however, were not randomized and included only small numbers of patients. In addition, no statistical analysis was performed.

6) GnRH analogues and danazol

Twenty-one RCT studies (Yee 1986; Henzl et al. 1988; Dmowski et al. 1989; Fedele et al. 1989; Henzl 1989; Tummon et al. 1989; Dawood et al. 1990; Henzl Kwei 1990; Kennedy et al. 1990; Miller 1990; Rolland and Heijden 1990; Fraser et al. 1991; Crosignani et al. 1992; NEET 1992; Shaw et al. 1992; Wheeler et al. 1992; Rock et al. 1993; Adamson and Pasta 1994; Cirkel et al. 1995; Odukoya et al. 1995; The A-Z Group 1996) and one cohort study (Miller et al. 1998) comparing the efficacy of GnRH analogues and danazol were eligible for our review.

These data did not provide a clear perspective on the effectiveness of these therapies. To clarify the results, we attempted to perform a

TABLE 4. Comparing of use of OC and GnRH analogues for treatment of the pain associated with endometriosis.

Authors (Year)	Type of study	OC group (Subjects)	GnRH group (Subjects)	Measurement parameter	Results (OC vs GnRH analogue group)	Statistics
Vercellini et al. (1993)	RCT	28	29	The 10-point pain scale value six months after treatment	7.5 ± 2.5 vs 7.4 ± 1.7	ns

Data indicated that OC were as effective as GnRH analogues for relief of the symptoms associated with endometriosis.

ns, not significant.

Table 5. Comparing of GnRH analogues and danazol as treatment for the pain associated with endometriosis.

Authors or study (Year)	Type of study	GnRH group (Subjects)	Danazol group (Subjects)	Measurement parameter	Results (GnRH vs danazol group)	Statistics
Zoladex study (1996)	RCT	35	36	Symptom relief rate	96.3% vs 71.4%	sig.
				Three-point pain scale value posttherapy	1.0 vs 3.0	ns
Cirkel et al. (1995)	RCT	30	25	Dysmenorrhea rate post-therapy	0% vs 0%	ns
				Dysmenorrhea rate six months after treatment	41.7% vs 25%	ns
Odukoya et al. (1995)	RCT	10	11	Three-point pain scale value post-therapy	1.0 vs 1.2	ns
Adamson et al. (1994)	RCT	90	34	Dysmenorrhea rate post-treatment	1% vs 6%	ns
				Dysmenorrhea rate six months after treatment	66% vs 50%	ns
Rock et al. (1993)	RCT	208	107	Three-point pain scale value post-therapy	1.4 vs 1.2	ns
				Three-point pain scale value six months after treatment	2.8 vs 2.4	ns
				Three-point pain scale value one year after treatment	3.3 vs 2.3	ns
Crosignani et al. (1992)	RCT	42	25	Symptom relief rates	not described	ns
NEET study (1992)	RCT	206	101	Moderate-to-severe pain post-therapy	17% vs 11%	ns
				Moderate-to-severe pain one year after treatment	23% vs 33%	ns
Shaw et al. (1992)	RCT	204	103	Three-point pain scale value post-therapy	1.2 vs 1.3	ns
				Three-point pain scale value six months after treatment	1.7 vs 2.3	ns
Wheeler et al. (1992)	RCT	134	136	Change in dysmenorrhea rate post-therapy	–99% vs –96%	ns
				Recurrence rate	67% vs 75%	ns
Fraser et al. (1991)	RCT	33	16	Three-point pain scale value post-therapy	0.3 ± 0.1 vs 0.3 ± 0.2	ns

Dawood et al. (1990)	RCT	209	101	Three-point pain scale value post-therapy	0.3 vs 0.2	ns
Henzl et al. (1990)	RCT	143	70	Symptom relief rate	91.5% vs 90%	ns
study 1				Moderate-to-severe pain rate	17% vs 11%	nd
study 2		104	63	Symptom relief rate	95% vs 94%	ns
				Moderate-to-severe pain rate	12% vs 14%	nd
Kennedy et al. (1990)	RCT	50	23	Symptom relief rate	94% vs 87%	ns
Miller (1990)	RCT	270*		Symptom relief rate	not described	nd
Rolland et al. (1990)	RCT	127	67	Moderate-to-severe pain rate	5% vs 29%	nd
Dmowski et al. (1989)	RCT	24	12	Three-point pain scale value post-therapy	0.7 ± 0.2 vs 0.4 ± 0.2	nd
Fedele et al. (1989)	RCT	30	32	Dysmenorrhea rate post-therapy	0% vs 0%	nd
				Dysmenorrhea rate six months after treatment	22% vs 27%	nd
				Dysmenorrhea rate one year after treatment	46% vs 50%	nd
				Recurrence rate one year after treatment	50% vs 47%	nd
Henzl (1989)	RCT	143	70	Moderate-to-severe pain rate	17% vs 11%	nd
				Fifteen-point pain scale value post-therapy	1.1 vs 1.0	nd
Tummon et al. (1989)	RCT	10	5	Ten-point pain scale post-therapy	0.4 ± 0.2 vs 1.4 ± 0.7	nd
Henzl et al. (1988)	RCT	156	80	Moderate-to-severe pain rate	25% vs 22%	nd
Yee (1986)	RCT	6	3	Symptom relief (subjects)	5 vs 2	nd
Miller et al. (1998)	Cohort	199	128	Time to recurrence (months)	5.2 vs 6.1	sig.

There was conflicting data concerning treatment effectiveness between the two therapeutic strategies in the identified RCTs.

Three-point, ten-point, and fifteen-point pain scales: linear scales on which 0 indicates the absence of pain and 3, 10, and 15 represent severe pain, respectively; sig., significant; nd, not defined; ns, not significant. *only the total number of participants was described.

TABLE 6. Meta-analysis comparing GnRH analogues and danazol as treatment for the pain associated with endometriosis.

Authors or study (Year)	GnRH group		Danazol group		Odds ratio	95% CI
	symptoms relieved (Subjects)	symptoms not relieved (Subjects)	symptoms relieved (Subjects)	symptoms not relieved (Subjects)		
Zoladex study (1996)	26	1	20	8	10.4	1.20-90.09
Kennedy et al. (1990)	47	3	20	3	2.35	0.44-12.66
Henzl et al. (1990) study 1	132	11	63	7	1.33	0.49-3.60
Henzl et al. (1990) study 2	99	5	59	4	1.34	0.35-5.20
Summary					2.0019	1.0471-3.8272

Our meta-analysis suggested the superiority of GnRH analogues over danazol for pain relief after six months of treatment.

meta-analysis. Four of the RCTs (Henzl and Kwei 1990 study 1, study 2; Kennedy et al. 1990; The A-Z Zoladex Group 1996) recorded symptom relief rates after six months of treatment. We combined these data using the Mantel-Haenszel method (Tables 5 and 6). This meta-analysis determined that GnRH analogues were more effective than danazol (OR = 2.0019, 95% CI = 1.0471-3.8272). We could not conduct meta-analysis with other RCTs due to the absence of such data as the mean differences in pain scale values.

In the identified RCTs, there were no significant differences after six months of treatment between the groups in overall pain (Shaw et al. 1992; Rock et al. 1993; Odukoya et al. 1995; The A-Z Zoladex Group 1996), dysmenorrhea (Wheeler et al. 1992; Adamson et al. 1994; Cirkel et al. 1995), pelvic pain (Wheeler et al. 1992; Cirkel et al. 1995), dyspareunia (Dawood et al. 1990; Fraser et al. 1991; Cirkel et al. 1995), pelvic tenderness (Dawood et al. 1990; Fraser et al. 1991), pelvic induration (Dawood et al. 1990; Fraser et al. 1991), or symptom relief (Crosignani et al. 1992). Six months after completing therapy, pain (Shaw et al. 1992; Rock et al. 1993), dysmenorrhea (Adamson et al. 1994; Cirkel et al. 1995), pelvic pain (Cirkel et al. 1995), dyspareunia (Cirkel et al. 1995), and pelvic tenderness (Cirkel et al. 1995) were similarly improved in both treatment groups over values seen for controls. One year after completion of treatment, there were no significant differences between the groups in overall pain (Rock et al. 1993), dysmenorrhea (Wheeler et al. 1992; NEET 1992), pelvic pain (NEET 1992), dyspareunia (NEET 1992), pelvic tenderness (NEET 1992), or pelvic induration (NEET 1992).

The cohort study (Miller et al. 1998) compared six-month GnRH analogue treatment with 6-month danazol treatment. There was a significant difference in the median time to recurrence of pain (5.2 months for the GnRH analogue group and 6.1 months for the danazol group, $p = 0.03$).

Thus, conflicting data in the identified RCTs made an evaluation of the efficacy of the two treatments ambiguous. Our meta-analysis, however, suggested superiority of GnRH analogues for pain relief following six months of treatment. The cohort study, however, suggested that danazol delayed the return of pain.

C. Combination management

1) Post-operative administration of OC

One RCT study (Muzii et al. 2000) examining post-operative low-dose administration of OC

TABLE 7. Results of post-operative treatment with OC for the pain associated with endometriosis.

Authors (Year)	Type of study	Therapy group (Subjects)	Control group (Subjects)	Measurement Parameter	Results (Therapy vs Control group)	Statistics
Muzii et al. (2000)	RCT	33	35	Recurrence rate during follow-up	9.1% vs 17.1%	ns
				Recurrence rate 12 months after treatment	6.2% vs 10.1%	sig.
				Recurrence rate 24 months after treatment	9.4% vs 13.6%	ns
				Recurrence rate 36 months after treatment	12.1% vs 17.4%	ns

Post-operative treatment with OC did not significantly reduce the recurrence of pain, although it did result in a delay in the recurrence of pain.

ns, not significant.

was eligible for our analysis (Table 7).

This RCT evaluated the effect of a six-month administration of periodic OC on the persistence and recurrence of pain symptoms after laparoscopic treatment for moderate to severe endometriosis with ovarian endometrioma. At follow-up, which occurred an average of 22 months after completing treatment, there was no significant difference in the recurrence rates of moderate-to-severe pain (9.1% in the OC group vs 17.1% in the placebo group). The mean time to recurrence of either symptoms or ovarian endometrioma was not significantly different (18.2 months vs 12.7 months). In life-table analysis, although the 12-month recurrence rate was significantly lower for the OC group than for the placebo group (6.2% vs 10.1%, respectively), no significant difference was evident at either 24 (9.4% vs 13.6%, respectively) or 36 months (12.1% vs 17.4%, respectively). While six-month administration of post-operative OC did not significantly reduce pain recurrence, a delay in the recurrence of pain was evident. A clinical trial (Vercellini et al. 2003) reported that long-term continuous OC can be used in women with endometriosis-associated recurrent dysmenorrhea that does not respond to cyclic OC use after surgical treatment.

A second RCT (Vercellini et al. 2002) compared the effectiveness of OC with that of cyproterone acetate in the treatment of endometriosis-associated recurrent pelvic pain after surgery. The results demonstrated that both treatments were effective.

2) Pre-operative administration of GnRH analogues

No studies examining the preoperative administration of GnRH analogues could be identified by our search. One RCT (Audebert et al. 1998), however, compared the effect of six-month preoperative administration of GnRH analogues with those of six-month post-operative administration of GnRH analogues. The effectiveness of the treatment and tolerance to treatment were similar in both groups.

3) Post-operative administration of GnRH analogues

We identified four RCT studies (Parazzini et al. 1994; Hornstein et al. 1997; Vercellini et al. 1999; Busacca et al. 2001) that evaluated the effectiveness of a three-month post-operative administration of GnRH analogues for the treatment of moderate to severe endometriosis (Table 8). One study (Busacca et al. 2001) compared three-month post-operative GnRH analogue administration after conservative surgery to expectant management alone. No differences were identified in the recurrence rates of moderate to severe pain during the follow-up period (6-36 months), cumulative pain recurrence rates at 18 months, or objective disease recurrence rates. The remaining RCT (Parazzini et al. 1994) compared three-month post-operative administration of GnRH analogues to placebo alone for the treatment of moderate to severe endometriosis. No difference could be identified between the groups in the mean reduction of the pain scores at 12

TABLE 8. Results of post-operative treatment with GnRH analogues for management of the pain associated with endometriosis.

Authors (Year)	Type of study	Therapy group (Subjects)	Control group (Subjects)	Measurement parameters	Results (Therapy vs Control group)	Statistics
Parazzini et al. (1994)	RCT	36	39	Change in the 10-point pain scale value nine months after treatment	–7.0 ± 4.1 vs –6.9 ± 4.6	ns
Busacca et al. (2001)	RCT	44	45	Recurrence rate during follow up	23% vs 24%	ns
				Recurrence rate 18 months after treatment	23% vs 29%	ns
Hornstein et al. (1997)	RCT	56	53	Rate at which alternative therapy was required	31% vs 57%	sig.
				Time until alternative therapy was required (months)	> 24 vs 11.7	sig.
				Change in the three-point pain scale value post-therapy	–3.2 ± 2.7 vs –1.0 ± 2.3	nd
				Change in the three-point pain scale value six months after treatment	–1.5 ± 2.7 vs –1.1 ± 2.6	nd
Vercellini et al. (1999)	RCT	133	134	Recurrence rate one year after treatment	13.1% vs 21.4%	ns
				Recurrence rate two years after treatment	23.5% vs 36.5%	ns
				Time to recurrence according to survival analysis	$\chi^2 = 4.19$ (therapy > control)	sig.

Six-month post-operative administration of GnRH analogues significantly delayed the time to pain recurrence after conservative surgery.

The ten-point pain scale is a linear scale on which 0 indicates the absence of pain and 10 represents severe pain; sig., significant; nd, not defined; ns, not significant.

months after surgery.

The effectiveness of six-month post-operative GnRH analogue administration for minimal to severe endometriosis was evaluated in two RCTs. The first (Vercellini et al. 1999) compared post-operative administration of a GnRH analogue after conservative surgery to expectant management. At the one- and two-year follow-up visits, no significant differences between the groups were observed in the recurrence rates of moderate or severe symptoms (after one year: 13.1% vs 21.4% for the GnRH analogues and expectant management groups, respectively, p = 0.143, OR = 0.55, 95% CI = 0.25-1.22; after two years: 23.5% vs 36.5% for the GnRH analogues and expectant management groups, respectively, p = 0.082, OR = 0.53, 95% CI = 0.25-1.14). A survival analysis indicated that the time to recurrence of symptoms was significantly longer in the GnRH analogue-treated group ($p = 0.041$).

A second RCT (Hornstein et al. 1997) compared post-operative administration of GnRH analogues after conservative laparoscopic surgery to placebo treatment. A significant increase in the median time to initiation of alternative treatment (> 24 months vs 11.7 months for the GnRH analogue and placebo groups, respectively) and decrease in the percentage of patients requiring alternative therapy (31% vs 57% for the GnRH analogue and placebo groups, respectively) were observed for the treatment group. Both groups demonstrated a statistically significant decrease in patient-reported pain scores from baseline to the end of treatment and at six months after treatment completion. While was a significant difference in the pain scores at the end of the treatment, there

was no significant difference six months after treatment. Only the GnRH analogue group exhibited a significant decrease in physician-reported pain scores at the end of the treatment and six months after treatment completion, a difference that was statistically significant at both time points.

In summary, three-month post-operative administration of a GnRH analogue did not significantly reduce the recurrence of pain caused secondary to moderate to severe endometriosis. In contrast, six-month post-operative administration of GnRH analogues significantly delayed the time to pain recurrence after conservative surgery in patients with minimal to severe endometriosis.

4) Post-operative administration of danazol

Three RCT studies (Telimaa et al. 1987a, b; Kauppila et al. 1989; Bianchi et al. 1999) examined the post-operative administration of danazol. Unfortunately, two of these RCTs were extremely similar, while the third used a different treatment method (Table 9).

The two similar RCTs (Telimaa et al. 1987a, b; Kauppila et al. 1989) compared six-month post-operative danazol or MPA administration with placebo treatment after conservative surgery for minimal to severe endometriosis. At follow-up 30 months after therapy completion, both the danazol and MPA groups exhibited significantly reduced pelvic pain in comparison with the placebo group. In addition, a significant difference was observed between these groups in the reduction of the symptom scores (55% reduction in the danazol group, 71% in the MPA group, and 26% in the placebo group).

The third RCT (Bianchi et al. 1999) compared three-month post-operative danazol with expectant management in patients with moderate to severe endometriosis. At follow-up visits (6-36 months), the recurrence rate of moderate to severe pelvic pain was 23% and 31% in the danazol and expectant management groups, respectively. The cumulative pain recurrence rates 12 months after surgery were 26% vs 34%, with objective recurrence rates of 8.3% and 15% in the danazol and expectant management groups, respectively. None of these differences were significant.

In summary, three-month post-operative danazol administration did not significantly reduce the recurrence of pain, although six-month post-operative danazol administration significantly reduced the incidence of pain recurrence associated with endometriosis. These results, however, are based primarily on a single study.

Discussion

Surgical treatment effectively relieves the pain associated with endometriosis in comparison to expectant management. However, 44.7% of

Table 9. Results from post-operative treatment with danazol for pain associated with endometriosis.

Authors (Year)	Type of study	Therapy group (Subjects)	Control group (Subjects)	Measurement parameters	Results (Therapy vs Control group)	Statistics
Bianchi et al. (1999)	RCT	36	41	Recurrence rate during follow up	23% vs 31%	ns
				Recurrence rate 12 months after treatment	26% vs 34%	ns
Kauppila et al. (1989)	RCT*	20	20	Change in the three-point pain scale value	–55% vs –26%	sig.
Telimaa et al. (1987)	RCT*					

Post-operative danazol administration for six months significantly reduced the recurrence of pain associated with endometriosis.

The three-point pain scale is a linear scale on which 0 indicates the absence of pain and 3 represents severe pain. sig., significant; nd, not defined; ns, not significant. *similar study designs.

patients continued to experience symptoms after surgery. Laparoscopic laser ablation with uterine nerve ablation is a standard method for the treatment of child-bearing women with endometriosis. It is difficult in cases in which the boundary between endometrial tissue and ovarian cortex is unclear. Although remnant disease or *de-novo* recurrence of the disease may lead to continuous symptoms after conservative surgical treatment, surgery is still a first-line option for the treatment of this disease.

Pharmacologic treatments effectively relieve the pain associated with endometriosis, however, there is insufficient evidence to address the long-term effects. There was too little data to evaluate the effectiveness of preoperative pharmacologic treatments, while evidence supporting post-operative pharmacologic treatments was not consistent.

The data from identified studies examining the relative effectiveness of GnRH analogues and danazol did not demonstrate a clear trend. The side effects of GnRH analogues and danazol, however, are different, which could influence treatment decisions. Although we tried to perform meta-analysis to determine which drugs should be used to manage endometriosis, there was insufficient data; we were only able to conduct meta-analysis by comparing the symptom relief rate of GnRH analogue treatment with that of danazol administration. Our meta-analysis with limited data indicated the effectiveness of GnRH analogues. We believe this result was observed because the number of RCTs evaluated was small, the trials were designed differently, and almost all the identified RCTs were published at least ten years ago with some lost raw data.

We attempted to contact many of the authors of these studies to collect the raw data. Of 34 letters sent, seven authors replied. Unfortunately, they did not provide any additional data that had not already been published. We could not contact two of the authors. Thus, the evaluation of the effect of treatments should be performed at an appropriate time.

Today, there is a paucity of data on the use of OC preparations for the treatment of symptomatic endometriosis (Moore et al. 2006). One trial suggested that OC were as effective as GnRH analogues (Vercellini et al. 1993), with less pronounced side effects than those seen in the GnRH analogue group. Although OC provide a promising treatment modality, further research is required to evaluate their roles in the management of endometriosis fully.

In conclusion, although both surgical and pharmacologic treatments are effective for relief of the pain associated with endometriosis, the recurrence rate of pain remains significant. The management of pain associated with endometriosis has thus not been satisfied. Larger unified clinical trials will be necessary to evaluate the effectiveness of new treatments are needed.

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