

## Review Article

# Laparoscopic Management of Endometriosis: Comprehensive Review of Best Evidence

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**ABSTRACT** **Study Objective:** To provide a comprehensive review of the best evidence available in the laparoscopic management of endometriosis for pain and/or fertility and to provide practical recommendations based on this information.

**Design:** Review article of randomized controlled trials.

**Patients:** Women with endometriosis.

**Methods:** A systematic search was performed of the Cochrane Library and MEDLINE database for randomized controlled trials relating only to laparoscopic management of endometriosis. The information from 7 Cochrane review articles and 35 original randomized trials is presented in a clinically relevant question-and-answer format.

**Conclusions:** Awareness of endometriosis as a disease with substantial morbidity is vitally important. Laparoscopic treatment of endometriosis is beneficial for reducing pain and improving fertility. Laparoscopic presacral neurectomy, but not laparoscopic uterosacral nerve ablation, is a useful adjunct to conservative surgery for endometriosis in patients with a midline component of pain. Preoperative hormonal suppression with gonadotropin-receptor hormone analogue may be helpful in decreasing endometriosis disease scores. Postoperative hormonal suppression with either a gonadotropin-receptor hormone analogue or progestin (including the levonorgestrel intrauterine system) may be helpful in reducing pain and increasing time to recurrence of symptoms. Excisional cystectomy is the preferred method to treat endometrial cysts for both pain and fertility and may be aided by the use of mesna and initial circular excision. An absorbable adhesion barrier (Interceed), 4% icodextrin solution (Adept), and a viscoelastic gel (Oxiplex/AP, FzioMed, Inc., San Luis Obispo, CA; not available in the United States) are safe and effective products to help prevent adhesions in laparoscopic surgery to treat endometriosis. *Journal of Minimally Invasive Gynecology* (2009) 16, 269–81 © 2009 AAGL. All rights reserved.

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Endometriosis occurs in 6% to 22% of women of reproductive age undergoing tubal ligation [1], 15% to 80% of women with chronic pelvic pain [2], and 21% to 65% of women evaluated because of infertility [3]. Fecundity in normal couples is about 15% to 20% and decreases with age [4], and is about 2% to 10% in women with untreated endometriosis and infertility [5]. Symptoms often do not correlate well with stage of endometriosis [6], and in the United States, the

mean time between onset of pain and the surgical diagnosis of endometriosis is about 12 years [7].

The criterion standard for the diagnosis of endometriosis is still considered by most to be direct visualization or histologic findings or both [8,9]. Endometriosis has a variety of appearances and forms including the classic “powder-burn” lesions, red lesions, white lesions, peritoneal retractions, and endometriotic cysts or “chocolate cysts” [10]. Endometriosis also may be associated with scar tissue and adhesions. A classification system that incorporates implant scores and adhesion scores has been developed by the American Society for Reproductive Medicine (r-ASRM) [11].

Treatment options for pain with endometriosis include medical and surgical interventions. Empiric use of a gonadotropin-receptor hormone analogue (GnRH agonist) has been tested in a single randomized controlled trial by Ling [12] in

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100 women with clinically suspected endometriosis. After 12 weeks of therapy with depot leuprolide acetate, 3.75 mg/mo, decreased dysmenorrhea and pelvic pain was noted in the treatment group. As a result, it has become common practice to administer empiric hormonal suppression therapy in patients with chronic pelvic pain. However, response to GnRH agonist incorrectly predicted the presence or absence of endometriosis in 14 of 44 patients (32%), and the author admits that GnRH agonist may cause improvement of symptoms from causes other than endometriosis. In a recent case-control study by Jenkins et al [13], 67% of patients with chronic pelvic pain who responded to hormonal therapy had histologically proved endometriosis, a rate equivalent to those without endometriosis. Thus, response to GnRH agonist is a poor predictor of endometriosis, and diagnostic laparoscopy (with histologic analysis) may still be required for the definitive diagnosis of endometriosis in the evaluation of pelvic pain [14].

Surgical treatment using laparoscopy or laparotomy is performed with the objective of destroying or removing visible areas of endometriosis and restoring normal anatomy. In some cases, adjunctive procedures that destroy nerve pathways thought to be responsible for the innervation of the pelvis are included in the management of pain. Laparoscopy has several advantages over laparotomy for the patient, in particular, faster recovery time. For the surgeon, laparoscopy offers 2 primary benefits, magnification and illumination, that are particularly helpful in the diagnosis of endometriosis [15]. Accurate diagnosis of endometriosis, in turn, is critical to effective surgical management.

Prevention of adhesions, whether de novo or by re-formation, is an important consideration in laparoscopic surgery in endometriosis because adhesions are thought to be related to infertility, possibly as a result of anatomic distortion [16]. Other consequences of adhesions may include dyspareunia, chronic abdominal or pelvic pain, and intestinal obstruction. The most common site of adhesion formation is the ovary [17]. For an adhesion to form, there must be contact between 2 areas of injury. Preventing contact between injured areas using some form of barrier of fluid agent can prevent adhesions. These agents should remain effective for 3 to 5 days to allow the peritoneum to become reestablished [18]. Barriers and fluid agents have been evaluated in the laparoscopic management of endometriosis and are summarized herein.

With proper technique and skill, laparoscopy is an ideal tool for management of endometriosis. Although there are several reviews of endometriosis, to our knowledge, none consolidate in a single place the best evidence for all of the issues that pertain to its laparoscopic management. The objective of the present study was to summarize the best evidence for the laparoscopic management of endometriosis in a way that is most clinically relevant and informative for surgeons.

## Materials and Methods

The Cochrane Library was searched using the terms “endometriosis” and “laparoscopy.” Reviews were selected that

pertained to the laparoscopic management of endometriosis and were analyzed for appropriate randomized trials. Original randomized trials were also searched for in MEDLINE from 1966 to the present using the following strategy: (1) exp laparoscopy/(43264), (2) exp endometriosis/(12019), (3) 1 and 2 (1409), and (4) limit 3 to (humans and randomized controlled trial). Only English-language articles were reviewed.

Inclusion criteria for studies selected for this review were that (1) the trial had to pertain to endometriosis diagnosed at either laparoscopy or histology; (2) the trial had to be properly randomized; and (3) the randomized intervention had to be either a laparoscopic technique or procedure, medical therapy before or after surgical management, or an adhesion prevention technique after laparoscopic management of endometriosis. Trials without proper randomization, that dealt with dysmenorrhea not associated with endometriosis, or that included laparotomy were excluded.

The trials were reviewed by all of the authors. The results are presented in question-and-answer format based on review of the information and on clinical concerns.

## Results

The search of the Cochrane Library produced 7 review articles [19–25], and MEDLINE search produced 68 articles. After exclusion, the data from 35 randomized trials were included in our review. In evaluating the results of the studies,  $P < .05$  was considered statistically significant. If a  $P$  value was not reported, a statistical difference was not assumed. If a difference or comparison was not statistically significant, then an attempt is made to determine whether an adequate sample size calculation was performed to detect the observed difference, with a power of at least 70%. For the purposes of this review, an intervention was considered clinically beneficial if the effect was statistically significant.

### *Pain Associated with Endometriosis*

*Is laparoscopy beneficial in treating pelvic pain associated with endometriosis?*

Yes, in all stages of endometriosis.

Two trials compared laparoscopic treatment of endometriosis with diagnostic surgery alone for pelvic pain (Table 1). In the classic study by Sutton et al, [26] 63 patients with mild to moderate endometriosis (r-ASRM stage I-III) were randomized to either the combination of ablation of implants with adhesiolysis and laparoscopic uterosacral nerve ablation (LUNA) or to diagnostic surgery only. At 6-month follow-up, the treatment group demonstrated a significantly greater improvement or complete resolution of symptoms according to visual analog scale (VAS) score (63% vs 33%). The benefits of laparoscopic treatment were poorest for stage I endometriosis, with only 38% of patients reporting improvement compared with 69% of patients with stage II disease and 100% of patients with stage III disease.

Table 1  
Effectiveness of conservative laparoscopic treatment of pelvic pain associated with endometriosis

Study	No. of patients	Randomization	Results*	Follow-up	Sig
Sutton et al [26], 1994	63	Ablation, adhesiolysis, and LUNA vs diagnostic only	63% vs 33%	6 mo	Yes <sup>†</sup>
Abbott et al [27], 2004	39	Delayed vs immediate	80% vs 32%	12 mo	Yes <sup>‡</sup>

LUNA = laparoscopic uterosacral nerve ablation; Sig = statistical significance.

\* Numbers represent percent pain-free according to visual analog scale score.

<sup>†</sup>  $P < .01$ , Fisher exact test.

<sup>‡</sup>  $P = .002$ , Mann-Whitney test.

The study by Abbott et al [27] confirmed these results. Thirty-nine patients with r-ASRM stage I to IV endometriosis were randomized to undergo either full excisional surgery (immediate group) or diagnostic surgery (delayed group). At a second laparoscopy at 6 months, significantly more patients in the immediate group exhibited improvement in VAS score and quality of life (80% vs 32%).

*Which is better for treatment of pain, laparoscopic excision or ablation?*

Not known.

A single study by Wright [28] addresses this issue (Table 2). Ablation was performed using monopolar diathermy at a coagulation current of 50 W. Excision was performed using 3-mm monopolar diathermy scissors at a combination current of 90 W. The sample size was small, and a power calculation was not performed. No significant difference in pain scores was noted after treatment. However, no definitive conclusions can be made because the study was likely underpowered to find any significant difference.

*Is laparoscopic uterosacral nerve ablation (LUNA) a useful adjunct in the laparoscopic management of pelvic pain with endometriosis?*

No, for all stages of endometriosis.

Three randomized trials addressed this question [29-31] (Table 3). Each trial randomized patients to undergo either laparoscopic conservative surgery to treat endometriosis plus LUNA, or conservative surgery alone. Patients with endometriosis r-ASRM stages I to IV were represented in the 3 trials. When conservative surgical management alone was compared with conservative management plus LUNA, there was no significant benefit to adding LUNA to the laparoscopic management of endometriosis-related pain in any of the 3 studies over the short and long terms regardless of initial r-ASRM stage or pain scores. The longest follow-up

was 36 months in most participants in the study by Vercellini et al [31].

*Is laparoscopic presacral neurectomy (LPSN) a useful adjunct to excision in the laparoscopic management of endometriosis-related pain?*

Yes, for all stages of endometriosis in patients with a midline component of pain.

Only 1 randomized trial addressed this question (Table 4). Zullo et al [32] randomized 141 patients with endometriosis r-ASRM stage I to IV to undergo either laparoscopic conservative surgery (ablation or excision) with LPSN or conservative surgery alone. Patients without a midline component of pain were excluded from the study. The cure rate was significantly higher in the group that underwent LPSN at 6-month follow-up (87.3% vs 60.3%) and at 12-month follow-up (85.7% vs 57.1%). The improvement in pain was maintained at 24 months in a follow-up study by the same group [33].

No difference was observed between the groups insofar as short-term complications. No long-term complication was detected in group A, whereas constipation and urinary urgency resulted in group B. In particular, constipation was reported in 21 (3.3%) and 9 (14.3%) patients after 6 and 12 months postintervention, respectively. In 15 of 21 patients (71.4%), constipation was treated successfully with medical therapy. At 6- and 12-month follow-up, urinary urgency was observed in 3 patients (4.8%).

### **Infertility Associated with Endometriosis**

*Is laparoscopic treatment beneficial for improving fertility in patients with endometriosis?*

Yes, in r-ASRM stages I and II.

Two randomized trials addressed this question (Table 5). The first and larger Canadian study by Marcoux et al [34]

Table 2  
Comparison between laparoscopic excision vs ablation in the treatment of pelvic pain

Study	No. of patients	Randomization	Results*	Follow-up	Sig <sup>†</sup>	Power <sup>‡</sup>
Wright, 2005	141	Excision vs ablation	11.2 vs 8.7	6 mo	NS	No

NS = not significant; Sig = statistical significance.

\* Average difference in pain score.

<sup>†</sup> Indicates whether a significant difference was present.

<sup>‡</sup> Indicates whether the sample size calculation was performed to detect the observed difference.

Table 3  
Effectiveness of LUNA as an adjunct in treating pelvic pain associated with endometriosis

Study	No. of patients	Randomization	Follow-up	Sig*	Power†
Johnson et al [29], 2004	67	LCS + LUNA vs LCS only	6 and 12 mo	NS	Yes
Sutton et al [30], 2001	51	LCS + LUNA vs LCS only	6 mo	NS	Yes
Vercellini et al [31], 2003	180	LCS + LUNA vs LCS only	1 and 3 yr	NS	Yes

LCS = laparoscopic conservative surgery; LUNA = laparoscopic uterosacral nerve ablation; NS = not significant; Sig = significance.

\* Indicates whether a significant difference was present.

† Indicates whether the sample size calculation was performed to detect the observed difference.

was a multicenter trial that included 25 sites. Three hundred forty-one infertile women aged 20 to 39 years with minimal or mild endometriosis (r-ASRM stage I or II) were randomized to undergo either conservative laparoscopic treatment of endometriosis by excision (laser) or ablation (electrocoagulation) or diagnostic surgery only. There was a benefit in the treatment group for fecundity (pregnancy rate, 4.7 vs 2.4 per 100 person-months) and in the cumulative probability of pregnancy (cumulative pregnancy rate, 30.7% and 17.7%, respectively, at 9 months). The participants were followed up for 36 weeks after laparoscopy or, for those who became pregnant, up to 20 weeks of pregnancy. Adjustment by other factors of infertility did not affect these results. On the basis of these results, 1 in 8 women would benefit from laparoscopic treatment of endometriosis.

In a second Italian study by Parazzini [35], 111 infertile women aged 36 years or younger with minimal to mild endometriosis (r-ASRM stage I or II) were randomized to undergo either resection or ablation of visible lesions or diagnostic laparoscopy only. There was no significant difference in pregnancy rate (followed to term) between the 2 groups at 1-year follow-up.

In both the Canadian and the Italian studies, baseline characteristics were similar by gynecologic and menstrual history, although only the Canadian study mentioned sperm analysis and laparoscopic findings.

### Medical Therapy in Conjunction with Surgery

#### *Is preoperative medical therapy beneficial in conjunction with conservative surgery?*

Perhaps. That is, preoperative GnRH agonist improved r-ASRM scores in patients with endometrial cysts, although the clinical benefit of this is not known.

Only 1 randomized trial addressed this question (Table 6). Donnez et al [36] included 80 infertile women younger than 35 years with endometrial cysts and peritoneal endometriosis confirmed at laparoscopy. All patients underwent a first and second laparoscopic procedure. In the first procedure, the de-

gree of endometriosis was assessed using the r-ASRM system, and all endometriotic cysts were opened. The patients were then randomized to receive either subcutaneous goserelin, 3.6 mg/mo for 12 weeks, or no treatment. At the second procedure 12 weeks later, the cyst wall and all endometrial lesions were vaporized using a carbon dioxide laser. There was a significant reduction in total r-ASRM scores and implant scores in the group that received the interim GnRH agonist compared with the control group at the second laparoscopic procedure but no significant difference in adhesion scores. Pain or pregnancy rate were not measured. Because of the design of this study, conclusions can only be made regarding r-ASRM scores.

#### *Does postoperative medical therapy in conjunction with conservative surgery to treat endometriosis improve outcomes?*

Perhaps there is a benefit for pain but not for pregnancy.

For the studies reviewed in this section, conservative surgery refers to either laparoscopic excision or ablation. Regardless, the surgery performed was equivalent in both groups, and the intervention that was randomized was the postoperative medical therapy.

Thirteen randomized trials addressed the issue of postsurgical medical therapy: 6 trials compared medical therapy with placebo [37–42] (Table 7); 5 trials compared medical therapy with no treatment [43–47] (Table 8), and 2 trials compared 2 different medical regimens [48,49] (Table 9) after conservative surgery to treat endometriosis. There was no statistically significant difference in pregnancy rate in any of these studies.

Hornstein et al [40] and Parazzini et al [41] both compared intranasal nafarelin therapy, 200 µg twice daily, with placebo. There was no difference in reduction of pain in either study. However, Hornstein et al demonstrated a significant advantage in the nafarelin-treated group in median time to requirement of alternative therapy for pain (>24 mo vs 11.7 mo). Telimaa et al [42] compared placebo with Danazol, 200 mg 3 times a day, and medroxyprogesterone acetate (MPA), 100 mg/d, for 6 months and found a significant difference in pain scores and implant scores for both Danazol

Table 4  
Effectiveness of LPSN as an adjunct in treating endometriosis-related pain

Study	No. of patients	Randomization	Results*	Follow-up	Sig†
Zullo et al [32], 2003	141	LCS + LPSN vs LCS only	87% vs 60%	12 mo	Yes

LCS = laparoscopic conservative surgery; LPSN = laparoscopic presacral neurectomy; Sig = significance.

\* Numbers indicate cure rate.

† Indicates whether a significant difference was present.

Table 5  
Effectiveness of laparoscopic treatment on infertility in endometriosis

Study	No. of patients	Randomization	Results	Follow-up	Sig*	Power†
Marcoux et al [34], 1997	341	Resection/ablation vs sham	31% vs 18% cPR	9 mo	Yes‡	—
Parazzini [35], 1999	111	Resection/ablation vs sham	24% vs 29% cPR	1 yr	NS	Yes

cPR = cumulative pregnancy rate; NA = data not available; NS, not significant; Sig = significance.

\* Indicates whether a significant difference was present.

† Indicates whether the sample size calculation was performed to detect the observed difference.

‡  $P = .006$ , log-rank test.

and MPA over placebo in 60 patients with primarily r-ASRM stage III or IV disease. Harrison and Barry-Kinsella [39] compared postoperative MPA, 50 mg/d, with placebo and found no statistical difference. Cobellis et al [38] compared a cyclooxygenase-2 antagonist rofecoxib, 25 mg/d, with placebo in 28 patients with r-ASRM stage I or II endometriosis and found a significant reduction in VAS pain scores at 6 months. Alborzi et al [37] compared postoperative pentoxifylline, 800 mg/d, with placebo and found no significant difference in pain or pregnancy rate.

Various postoperative medical therapies have been compared with surgery alone. Bianchi et al [43] used postoperative Danazol, 600 mg/d; Busacca et al [44], Loverro et al [45], and Vercellini et al [47] used postoperative GnRH agonist (intramuscular leuprolide, 3.75 mg/mo; intramuscular triptorelin, 3.75 mg/mo; and subcutaneous goserelin, 3.6 mg/mo, respectively); and Muzii et al [46] used postoperative low-dose oral contraceptives (ethinyl estradiol, 0.03 mg/d, and gestadone, 0.075 mg/d, for 21 days followed by a 7-day interval). There was no statistically significant difference in pain reduction, pregnancy rate, or disease scores in any of these studies. However, Vercellini et al [47] did find at survival curve analysis a significantly longer time to recurrence of pain in the goserelin-treated group (about 24% in the expectant group vs 18% in the goserelin group at 24 months).

Regidor et al [49] compared the postoperative use of the subcutaneous GnRH agonist leuprorelin, 3.75 mg/mo, with the progestin lynestrenol, 5 mg twice daily, postoperatively and found no statistically significant difference in pain reduction or disease score. Cosson et al [48] reported the same findings comparing postoperative dienogest, 1 mg/d, a progestin, and intramuscular GnRH agonist triptorelin, 3.75 mg/mo.

*How does perioperative medical therapy compare with post-surgical medical therapy in conjunction with conservative surgery to treat endometriosis?*

No difference in pain scores; however, preoperative GnRH agonist lowered r-ASRM scores.

Two randomized trials addressed this question (Table 10). Audebert et al [50] randomized 55 patients with stage III or IV endometriosis to receive either intranasal nafarelin, 200 $\mu$ g twice daily, for 6 months followed by laparoscopic treatment, or laparoscopic treatment followed by 6 months of intranasal nafarelin. All patients underwent follow-up laparoscopy at 6 months. There was no difference in pain scores. The group that received preoperative GnRH agonist had a significant reduction in total r-ASRM and independent adhesion scores. However, whether preoperative medical therapy facilitated surgery could not be determined.

Batioglu et al [51] randomized 26 patients with laparoscopically proved endometrial cysts greater than 3 cm to undergo either surgical treatment by drainage followed by 6 months of intramuscular GnRH agonist leuprorelin, 3.75 mg/mo, or preoperative GnRH agonist for 6 months followed by drainage at second laparoscopy. Drainage of the cyst followed by GnRH agonist for 6 months was more effective in reducing r-ASRM scores for the endometrial cysts compared with GnRH agonist alone. There was, however, no difference in pregnancy rate between the 2 groups.

*Does the use of a levonorgestrel intrauterine system (LNG-IUS) after conservative surgery for endometriosis improve pain?*

Yes.

Only 1 randomized trial addressed this question (Table 11). Vercellini et al [52] randomized 40 patients with symptomatic stage III or IV endometriosis to either LNG-IUS insertion or expectant management after laparoscopic treatment. There was a significant reduction in pain recurrence (10% vs 45%) with the LNG-IUS. The authors concluded that the LNG-IUS would prevent recurrence of pain associated with moderate to severe endometriosis in 1 of 3 patients (number needed to treat, 3). The study was designed as a pilot study; therefore, the sample size was small, and larger trials would add strength to the results. However, the pain reduction in the LNG-IUS group was statistically

Table 6  
Effectiveness of preoperative medical therapy in conjunction with conservative laparoscopic surgery in endometriosis

Study	No. of patients	Randomization	End point	Follow-up	Sig*
Donnez et al [36], 1994	80	SC goserelin vs none	r-ASRM score	3 mo	Yes†

r-ASRM = revised classification system of the American Society for Reproductive Medicine; SC = subcutaneous; Sig = significance.

\* Indicates whether a significant difference was present.

†  $P < .01$  for total r-ASRM score;  $P < .05$  for r-ASRM implant score,  $\chi^2$  test.

Table 7

Effectiveness of postoperative medical therapy vs placebo in conjunction with conservative laparoscopic surgery for endometriosis-related pain

Study	No. of patients	Randomization	End point	Follow-up	Sig*	Power <sup>†</sup>
Telimaa et al [42], 1987	60	Danazol, MPA, placebo	Pain, r-ASRM	6 mo	Yes <sup>‡</sup>	—
Parazzini et al [41], 1994	75	GnRHa for 3mo vs placebo	Pain, PR	12 mo	NS	No
Hornstein et al [40], 1997	109	GnRHa for 6mo vs placebo	Time to recurrence	24 mo	Yes <sup>§</sup>	—
Harrison and Barry-Kinsella [39], 2000	100	MPA for 3mo vs placebo	Pain, PR, rASRM	3 mo	NS	Yes
Cobellis et al [38], 2004	28	COX-2 for 6mo vs placebo	Pain	6 mo	Yes <sup>  </sup>	—
Alborzi et al [37], 2007	88	Pentoxifylline vs placebo	Pain, PR	1 yr	NS	No

COX = cyclooxygenase; MPA = medroxyprogesterone acetate; NA = data not available; NS = not significant; PR = pregnancy rate; r-ASRM = revised classification of the American Society for Reproductive Medicine; Sig = significance.

\* Indicates whether a significant difference was present.

<sup>†</sup> Indicates whether the sample size calculation was performed to detect the observed difference.

<sup>‡</sup> For MPA and Danazol vs placebo,  $P < .001$  for reduction of pain.

<sup>§</sup>  $P = .001$ , Wilcoxon test.

<sup>||</sup>  $P < .0001$ , Kriskall-Wallis test.

significant, and the small number needed to treat of 3 makes the results clinically significant also.

### Endometrial Cysts

*Which surgical technique is better for treating endometrial cysts, excision or fenestration and coagulation?*

Excision is better for pain and pregnancy.

Two randomized trials addressed this question (Table 12). Beretta et al [53] randomized 64 patients with endometrial cysts greater than 3 cm to undergo either cystectomy or fenestration and coagulation. The group treated with excision had a significantly longer median time to recurrence of symptoms (19.0 months vs 9.5 months) and a significantly higher spontaneous pregnancy rate (24-month cumulative pregnancy rate, 66.7% vs 23.5%). Alborzi et al [54] randomized 100 patients with symptomatic (infertility or pain) endometrial cysts to either cystectomy or fenestration and coagulation. The group that underwent cystectomy had a significantly lower recurrence of symptoms at 2 years (15.8% vs 56.7%), a significantly higher cumulative pregnancy rate at 1 year (59.4% vs 23.3%), and a significantly lower rate of second operations (5.8% vs 22.9%).

Note that although the patients in both studies were followed up for cyst recurrence with transvaginal ultrasound at 3, 6, 12, and 24 months, the strength of these studies is

that the primary end points are outcomes that matter to patients: pain recurrence and pregnancy rate (defined as an intrauterine gestational sac at transvaginal ultrasonography).

*Does excision or cystectomy negatively affect pregnancy rate in controlled ovarian hyperstimulation in patients with endometriosis?*

No.

Only 1 randomized trial directly addressed this question (Table 13). Alborzi et al [55] randomized 81 patients with endometrial cysts and infertility to either cystectomy or fenestration and coagulation, followed by 1 or 2 cycles of controlled ovarian hyperstimulation. The mean number of dominant follicles and the pregnancy rate were equivalent. Follow-up was not long enough to determine take-home pregnancy rate.

*Are there techniques that can improve laparoscopic cystectomy?*

Yes, mesna (sodium-2-mercaptoethanesulfonate) and initial circular excision.

Two interesting randomized trials are considered here (Table 14). Benassi et al [56] randomized 44 patients with symptomatic endometrial cysts to undergo either laparoscopic cystectomy with the aid of mesna (a chemical mucolytic) or cystectomy with the aid of isotonic sodium

Table 8

Effectiveness of postoperative medical therapy vs none in conjunction with conservative laparoscopic surgery for endometriosis-related pain

Study	No. of patients	Randomization	End point	Follow-up	Sig*	Power <sup>†</sup>
Bianchi et al [43], 1999	77	Danazol for 3 mo vs none	Pain, PR, r-ASRM	3 yr	NS	No
Vercellini et al [44], 1999	269	GnRHa for 6 mo vs none	Time to recurrence	2 yr	Yes <sup>‡</sup>	—
Muzii et al [46], 2000	70	OC for 6 mo vs none	Pain, time to cyst recurrence	22 mo	NS	Yes
Busacca et al [44], 2001	89	GnRHa for 3 mo vs none	Pain, PR, r-ASRM	3 yr	NS	Yes
Loverro et al [45], 2001	62	GnRHa for 3 mo vs none	Pain, PR	NA	NS	No

GnRHA = gonadotropin-receptor hormone analogue; NA = data not available; NS = not significant; OC = oral contraceptive; PR = pregnancy rate; r-ASRM = revised classification of the American Society for Reproductive Medicine; Sig = significance.

\* Indicates whether a significant difference was present.

<sup>†</sup> Indicates whether the sample size calculation was performed to detect the observed difference.

<sup>‡</sup>  $P = .041$ , survival curve analysis.

Table 9

Effectiveness of comparing 2 postoperative medical regimens in conjunction with conservative laparoscopic surgery to treat endometriosis-related pain

Study	No. of patients	Randomization	Results	Follow-up	Sig*	Pwr <sup>†</sup>
Regidor et al [49], 2001	48	GnRHa vs progestin	Pain, r-ASRM	6 mo	NS	No
Cosson et al [48], 2002	142	Progestin vs GnRHa	Pain, r-ASRM	4 mo	NS	Yes

GnRHa = gonadotropin-receptor hormone agonist; NS = not significant; r-ASRM = revised classification of the American Society for Reproductive Medicine; Sig = significance.

\* Indicates if a significant difference was present.

† Indicates whether the sample size calculation was performed to detect the observed difference.

chloride solution. Compared with saline solution, mesna resulted in significant reductions in operating time (49 vs 70 min), perceived difficulty (9% vs 91% difficulty rating), and reduced blood loss (1.2 vs 1.7 hemoglobin decrease).

Muzii et al [57] randomized 48 patients with endometrial cysts to either circular excision and subsequent stripping or immediate stripping. Circular excision and subsequent stripping seemed to be more easily performed than direct stripping, although operative times were comparable for the 2 techniques. A second randomization occurred at the ovarian hilus, stripping vs coagulation and cutting; however, there was no difference in ease of the procedure or operating time.

### Adhesion Prevention

*Are adhesion barriers useful in the laparoscopic treatment of endometriosis?*

Yes, for re-formed adhesions.

Only 1 randomized trial directly addressed the issue of adhesion barriers in laparoscopic surgery to treat endometriosis (Table 15). Mais et al [59] randomized 32 patients with stage III or IV endometriosis and complete posterior cul-de-sac obliteration and who were undergoing laparoscopic surgery to either surgery alone or surgery and application of an absorbable adhesion barrier (Gynecare Interceed; Ethicon Women's Health and Urology, Somerville, New Jersey). A second laparoscopy performed 12 to 14 weeks after the initial surgery demonstrated a significant reduction in adhesion reformation (75% adhesion-free vs 12.5%) in the group receiving Interceed vs no adhesion barrier. All patients received 3 months of GnRH agonist therapy postoperatively. There was no conflict of interest of the authors of this study. Note that although the sample size in this single study was small, the results were significantly different (with a large

absolute difference in patients who were adhesion-free); thus, the results are valid. However, larger trials are needed to further confirm these results.

*Are fluid or pharmacologic agents useful in the laparoscopic treatment of endometriosis?*

Yes.

Two randomized trials directly addressed this question (Table 16). Brown et al [60] randomized 402 patients with primary diagnoses including endometriosis, pelvic pain, and infertility to receive either 4% icodextrin solution (Adept Adhesion Reduction Solution; Baxter Biosurgery, Deerfield, Illinois) or lactated Ringer's solution intraoperatively. Adhesions were scored by a classification system developed in consultation with the US Food and Drug Administration (FDA) and included the incidence (23 locations were evaluated), extent (defined in thirds of the anatomical site covered), and severity (defined as filmy and avascular vs dense or vascular) of adhesions; the American Fertility Society adhesion scoring was also used. Adhesions were evaluated at initial laparoscopy and at second laparoscopy 4 to 8 weeks later, in a double-blinded manner. Double blinding was possible because both fluid agents used are clear and odorless. The authors videotaped all procedures and ensured that the adhesion scores after video review matched the adhesion scores at the time of procedure. Significantly more patients who received Adept demonstrated a reduction in adhesion scores compared with those who received lactated Ringer solution; clinical success was achieved in 39% vs 15% of patients with endometriosis, and 54% vs 25% in patients with both endometriosis and infertility. Clinical success was defined as the number of sites with adhesions decreased by at least 3 or 30% of the number of sites lysed. There was no benefit in VAS pain scores, and pregnancy rate was not measured.

Table 10

Effectiveness of perioperative medical therapy in conjunction with conservative laparoscopic surgery for endometriosis-related pain

Study	No. of patients	Randomization	Results	Follow-up	Sig*	Power <sup>†</sup>
Audebert et al [50], 1998	55	Pre vs post-op GnRHa	Pain, r-ASRM	6 mo	NS	No
Batioglu et al [51], 1996	26	Preoperative vs perioperative GnRHa	r-ASRM, PR	6 mo	NS	No

GnRHA = gonadotropin-receptor hormone analogue; NS = not significant; PR = pregnancy rate; r-ASRM = revised classification of the American Society for Reproductive Medicine; Sig = significance.

\* Indicates whether a significant difference was present.

† Indicates whether the sample size calculation was performed to detect the observed difference.

Table 11

Effectiveness of postoperative LNG-IUS therapy in conjunction with conservative laparoscopic surgery for endometriosis-related pain

Study	No. of patients	Randomization	Results	Follow-up	Sig*
Vercellini et al [52], 2003	40	LNG-IUS vs expectant therapy	10% vs 45%	1 yr	Yes <sup>†</sup>

LNG-IUS = levonorgestrel intrauterine system; Sig = significance.

\* Indicates whether a significant difference was present.

†  $P = .03$ , Fisher exact test.

diZerega [61] randomized 37 patients with stage I to III endometriosis (patients with endometrioma only were excluded) to either adhesion barrier gel treatment (Oxiplex/AP; FzioMed, Inc, San Luis Obispo, California) after laparoscopic surgical treatment of endometriosis or surgery alone. At second laparoscopy 6 to 10 weeks later, there was an increase in adhesion scores in the patients who underwent surgery only; however, there was a significant decrease in the adhesion scores in patients who received Oxiplex/AP. Further, there was a greater increase in adhesion scores when red lesions were present in the group that underwent surgery alone. There was no conflict of interest of the authors in either of these studies.

## Discussion

### Pain Associated with Endometriosis

There are 2 kinds of dysmenorrhea, primary and secondary. Primary dysmenorrhea is pain without an identifiable anatomical cause. The exact cause of primary dysmenorrhea is a source of debate; however, overproduction of prostaglandins has been identified as a contributing factor [62]. In secondary dysmenorrhea an identifiable cause such as endometriosis or adenomyosis is present. In our review, we focused only on the laparoscopic treatment of secondary dysmenorrhea caused by endometriosis.

Two randomized trials [26,27] clearly demonstrate that laparoscopic treatment is beneficial compared with diagnostic surgery alone for endometriosis related pain. The magnitude of benefit from laparoscopic surgery, that is, reducing pain from 63% to 33% [26] and from 80% to 32% [27], make it an option that should be considered in patients with pain suspicious for endometriosis. However, it is not possible to determine whether excision or ablation of endometrial lesions is superior.

In a study by Sutton et al [26], LUNA was combined with ablation of lesions and adhesiolysis. Thus, it was not possible

to differentiate the effects of the individual components of surgery, and conclusions can be based only on the combination of these interventions. The benefit of laparoscopic management was continued at 18 months [63] and up to 6 years [64]. In the study by Abbott et al [27], surgery was performed by excision alone. Although the magnitude of the effect of excision in the study by Abbott and coworkers is greater than the combination of techniques in the study by Sutton and colleagues, a direct comparison cannot be made. The follow-up in the study by Abbott and coworkers was 1 year.

The benefits of laparoscopic surgery were less for stage I endometriosis in the study by Sutton et al [26]. The authors of that study offer 2 possible explanations for this finding. First, there may have been underdiagnosis of atypical lesions of endometriosis in patients with stage I disease, and second, patients with mild endometriosis may have lesions that infiltrate deeper and are inadequately treated using laser ablation.

A placebo effect of diagnostic laparoscopy on endometriosis-related pain was noted in both studies cited. Again, Sutton et al [26] offer several possible explanations for this effect seen clearly in their study at 3 months but not at 6 months after surgery. It may be that procedures that are presented as technologically advanced have a positive effect on subjective symptoms such as pain. Perhaps performance of laparoscopy or suctioning of the pelvic fluid to adequately visualize the posterior cul-de-sac is therapeutic for pain.

There was no demonstrable benefit of LUNA as an adjunct in secondary dysmenorrhea associated with endometriosis. However, other randomized trials demonstrate a significant benefit of LUNA as an adjunct in treating primary dysmenorrhea [65].

Another useful adjunct to the laparoscopic treatment of endometriosis in patients with a midline component of pain is LPSN, with patients experiencing improvement in both midline and lateral pain. This is a more difficult procedure to perform and requires technical expertise and knowledge of the presacral anatomy. Patient selection and counseling

Table 12

Effectiveness of laparoscopic cystectomy over fenestration and coagulation for treatment of endometrial cysts

Study	No. of patients	Randomization	End point	Follow-up	Sig*
Beretta et al [53], 1998	64	Excision vs fenestration	Pain, cPR	2 yr	Yes <sup>†</sup>
Alborzi et al [54], 2004	100	Excision vs fenestration	Pain, cPR	2 yr	Yes <sup>‡</sup>

cPR = cumulative pregnancy rate; Sig = significance.

\* Indicates whether a significant difference was present.

†  $P < .05$ , generalized Wilcoxon survival test for both pain and cPR.‡  $P < .001$  for pain reduction, Fisher exact test;  $P < .009$  for cPR.

Table 13  
Effectiveness of laparoscopic cystectomy on controlled ovarian hyperstimulation

Study	No. of patients	Randomization	End point	Follow-up	Sig*	Power <sup>†</sup>
Alborzi et al [55], 2007	81	Excision vs fenestration	PR, COH	2 mo	NS	No

COH = controlled ovarian hyperstimulation; NS = not significant; PR = pregnancy rate; Sig = significance.

\* Indicates whether a significant difference was present.

<sup>†</sup> Indicates whether the sample size calculation was performed to detect the observed difference.

is important with the use of LPSN. Long-term complications were primarily constipation (14%) and urinary urgency (5%) at 12 months. Most of these complications responded to medical therapy.

These studies emphasize the utility of laparoscopy in the management of pelvic pain associated with endometriosis.

### Infertility Associated with Endometriosis

Surgery is beneficial in improving fertility in patients with endometriosis. In contrast, medical therapy is not effective for increasing fertility in patients with endometriosis. The effect of laparoscopic surgery on pregnancy rate from in vitro fertilization has not been studied in randomized controlled trials and, thus, is not specifically addressed in this review.

Although the studies by Marcoux et al [34] and Parrazini et al [35] reached conflicting conclusions, meta-analysis [66] of these 2 studies indicated that there is a significant benefit of conservative laparoscopic surgery to enhance fecundity in infertile women aged up to 35 to 39 years with r-ASRM stage I or II endometriosis. This meta-analysis suggested that the number needed to treat is between 3 and 100.

### Medical Therapy in Conjunction with Surgery

The results in the trials in this category are more difficult to sort out because studies differ in terms of medical therapy used, population investigated, and study end points. There is no benefit of medical therapy in conjunction with surgery for improving fertility. Overall, there is insufficient evidence to make a clear conclusion that there is any benefit of medical therapy in conjunction with surgery to treat pain [25]. None of the studies reported quality-of-life measures that are clin-

ically important because the adverse effects associated with medical therapies can be substantial. However, some helpful information can be teased from these studies.

Presurgical GnRH agonist showed benefit in reducing r-ASRM scores in some studies [36,50,51]. However, lower endometriosis disease scores may or may not be associated with better clinical outcome for patients or surgeons, such as ease and duration of surgery, and patient satisfaction. Further, it is not known whether the lower r-ASRM scores are a result of reduction in disease or of a changed appearance. Some authors have suggested that presurgical hormonal suppression may render the endometriotic lesions more difficult to visualize and subsequently lead to a higher recurrence rate [67]. There may be some benefit of postsurgical hormonal suppression with GnRH agonist in extending time to recurrence of pain at 2 years, as reported by Hornstein et al [40] and Vercellini et al [47]. Cyclooxygenase-2 antagonists or progestin may reduce pain up to 6 months after laparoscopic treatment, whereas the LNG-IUS may be effective for up to 1 year after surgery.

### Endometrial Cysts

Drainage alone to treat endometrial cysts is not recommended because of the high recurrence rate [36]. Based on our review, excision at cystectomy is superior to fenestration and coagulation for treatment of pain (reflected in less pain and longer time to recurrence of symptoms) and for pregnancy (reflected in cumulative pregnancy rates) [53,54]. It is possible that excision at cystectomy might negatively affect the success of controlled ovarian hyperstimulation by removing normal ovarian tissue [68,69]. However, the mean

Table 14  
Effectiveness of different techniques for performing laparoscopic endometrial cystectomy

Study	No. of patients	Randomization	End point	Follow-up	Sig*	Power <sup>†</sup>
Benassi et al [56], 2003	44	Mesna vs saline solution	Time of operation, ease of operation, blood loss	2 d	Yes <sup>‡</sup>	—
Muzii et al [57], 2005 Part 1	48	Start: circular excision vs immediate stripping	Ease of operation	Time of operation	Yes <sup>§</sup>	—
Muzii et al [58] 2005 Part 2	48	End: stripping vs coagulation and cutting	Time of operation, ease of operation	Time of operation	NS	No

NA = data not available; NS = not significant; Sig = significance.

\* Indicates whether a significant difference was present.

<sup>†</sup> Indicates whether the sample size calculation was performed to detect the observed difference.

<sup>‡</sup>  $P < .05$ ,  $\chi^2$  test;  $P < .001$ , Fisher exact test;  $P < .05$ , Mann-Whitney test.

<sup>§</sup>  $P < .01$ , Fisher exact test.

Table 15  
Effectiveness of absorbable barrier (Interceed) for adhesion prevention in laparoscopic management of endometriosis

Study	No. of patients	Randomization	Results	Follow-up	Sig*
Mais et al [59], 1995	32	Interceed vs none	75% vs 13% adhesion-free	3 mo	Yes <sup>†</sup>

Sig = significance.

\* Indicates whether a significant difference was present.

<sup>†</sup>  $P < .05$ , Fisher exact test.

number of dominant follicles and pregnancy rate do not seem to be affected by cystectomy [55].

Mesna is a mucolytic and can act as a chemical dissector. After incising the capsule and exposing the cyst, mesna was applied drop by drop directly on the cyst walls. While steady traction was applied to the brim of the cyst wall, additional solution was added until the cyst was completely detached. Benassi et al [56] found that using mesna made cystectomy easier and resulted in shorter operating times and less blood loss.

Muzii et al [57] demonstrated that cystectomy was easier with circular excision of the ovarian capsule followed by stripping rather than immediate stripping. Circular excision involves resecting a disk of ovarian tissue around the initial cyst adhesion site to begin the stripping procedure through tissues that are less densely adherent to each other. With immediate or direct stripping, the cyst wall was stripped starting at the original adhesion site where ovarian parenchyma and cyst wall are thin and densely adherent to each other.

### Adhesion Prevention

Synthetic barriers have been developed for adhesion prevention. Interceed barrier is an oxidized regenerated cellulose compound. It can be cut as necessary, requires no suturing, can be applied laparoscopically, and is absorbable. It is an FDA-approved adhesion barrier for use in laparotomy. Interceed absorbs water and sticks to any surface. It forms a gelatinous protective coat within 8 hours and is absorbed within 2 weeks. Interceed must be applied after hemostasis is achieved because it is a procoagulant and causes fibrin deposition at sites of incomplete hemostasis. Interceed saturated with blood, therefore, increases the likelihood of subsequent adhesion formation. Its failure to prevent adhesions in some circumstances has been ascribed to possible migration [20].

The only trial that addressed barriers for adhesion prevention after laparoscopic treatment of endometriosis

was by Mais et al [59]. There was a significant reduction in re-formation of adhesions with the use of Interceed. Alternative approaches may be needed in instances of de novo adhesions and adhesions at the adnexae [70–72].

Fluid or pharmacologic agents have been used to prevent adhesions. Adept (4% icodextrin solution) is the only FDA-approved fluid agent for adhesion prevention in laparoscopy in the United States. Icodextrin is an  $\alpha$ -1,4-glucose polymer of high molecular weight. It is colorless, nonviscous, iso-osmolar, and instilled intraperitoneally at the conclusion of surgery. It requires at least 4 days for complete absorption. Adept significantly reduced adhesion scores in the laparoscopic treatment of endometriosis [60]. The benefit in adhesion prevention was more pronounced in patients with endometriosis and infertility. It is considered safe, although there was an increase in the incidence of transient labial edema.

Oxiplex/AP, a viscoelastic gel composed of polyethylene oxide and carboxymethylcellulose, is effective in reducing adhesion scores in the laparoscopic treatment of endometriosis [61]. Oxiplex is an innovative polymer material that is formulated for a variety of indications including postsurgical adhesions, drug delivery, and hemostasis. It is currently not commercially available in the United States.

### Author Conclusions

#### Summary of Recommendations for Practice

Awareness of endometriosis as a disease with substantial morbidity is vitally important, especially in patients with chronic pelvic pain. Laparoscopy is an ideal tool for the diagnosis and treatment of endometriosis because it affords the benefits of magnification and illumination. Laparoscopic treatment of endometriosis is beneficial for reducing pain and improving fertility. Laparoscopic presacral neurectomy, but not LUNA, is a useful adjunct to conservative surgery to

Table 16  
Effectiveness of fluids or pharmacologic agents for adhesion prevention in laparoscopic management of endometriosis

Study	N	Randomization	Results	Follow-up	Sig*
Brown et al [60], 2007	402	Adept vs LRS	39% vs 15% <sup>†</sup>	2 mo	Yes <sup>‡</sup>
diZerega et al [61], 2007	37	Oxiplex/AP vs none	Decreased vs increased adhesions	2 mo	Yes <sup>§</sup>

LRS = lactated Ringer's solution; Sig = significance.

\* Indicates whether a significant difference was present.

<sup>†</sup> Clinical success was defined as number of sites with adhesions decreased by at least 3 or 30% of the number of sites lysed.

<sup>‡</sup>  $P = .036$ , analysis of covariance.

<sup>§</sup>  $P < .01$ , signed rank test.

treat of endometriosis in patients with a midline component of pain. Knowledge and skill for treating endometriosis at laparoscopy is increasingly becoming an area of subspecialization [73].

Preoperative hormonal suppression with GnRH agonist may be helpful in reducing disease scores. Postoperative hormonal suppression with either GnRH agonist or progestin, including the LNG-IUS, may be helpful in reducing pain and increasing time to recurrence of symptoms. Excisional cystectomy is the preferred method to treat endometrial cysts for both pain and fertility and may be aided by the use of mesna and initial circular excision. Barriers or fluids may be used to reduce adhesion formation but cannot replace good surgical technique. Interceed and Adept are safe and effective products to prevent adhesions in laparoscopic surgery to treat endometriosis. Oxiplex/AP is effective in reducing adhesions after laparoscopic management of endometriosis but is not yet available in the United States.

#### Summary of Recommendations for Research

There is a need for good quality and adequately powered trials. Primary end points should include pain and pregnancy rate. Trial design should include double blinding if possible, proper randomization, and long-term follow-up (at least 1 year). Placebo arms should be included, as well as valid measurements of outcomes such as VAS score for pain and quality-of-life measures. Inclusion criteria should include histologic analysis, when possible, for the diagnosis of endometriosis.

Currently, there are no randomized trials that address the question of whether laparoscopic surgery is more effective than medical treatment for pain associated with endometriosis. In addition, there are no adequately powered randomized trials to answer the question of whether excision or ablation of endometrial lesions is the superior technique. There is a need for good quality trials to answer these important questions.

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