SCIENTIFIC PAPER

A Pilot Feasibility Multicenter Study of Patients After Excision of Endometriosis

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ABSTRACT

Objective: To serve as a pilot feasibility study for a randomized study of excision versus ablation in the treatment of endometriosis by (1) estimating the magnitude of change in symptoms after excision only at multiple referral centers and (2) determining the proportion of women willing to participate in a randomized trial.

Methods: We performed a multicenter prospective study of women undergoing excision for endometriosis (Canadian Task Force class II-3) at Duke University Center for Endometriosis Research & Treatment (currently the Saint Louis University Center for Endometriosis), Center for Endometriosis Care, Northshore University Health System, Memorial University (Canada), and Florida Hospital. The study comprised 100 female patients, aged 18 to 55 years, with endometriosis-suspected pelvic pain. The intervention was laparoscopic excision only of the abnormal peritoneum suspicious for endometriosis. The main outcome measures were quality of life, pelvic pain, dysmenorrhea, dyspareunia, and bowel and bladder symptoms.

Results: The mean follow-up period was 8.5 months. Excision of endometriosis showed a significant reduction in all pain scores except bowel symptoms, as well as significant improvement in quality of life. Of the patients, 84% were willing to participate in a randomized study.

Conclusions: Quality of life is a needed primary outcome for any randomized study comparing excision versus ablation. A multicenter comparative trial is feasible, although quality assurance would have to be addressed. Patients were willing to be randomized even at surgical referral centers.

Key Words: Endometriosis, Excision, Ablation, Randomized study, Quality of life.

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INTRODUCTION

The optimal technique for the surgical management of peritoneal endometriosis is not clear. Two main categories of surgical management exist and are referred to as ablation (where endometrial implants are destroyed with energy, which will include vaporization, without a specimen being taken out of the body) and excision (where the implant is completely removed from the body and sent to the pathology department). There is little evidence from randomized controlled trials (RCTs) to guide surgical management of endometriosis-associated pelvic pain. In the classic RCT by Sutton et al.[1] published in 1994, the combination of laparoscopic ablation and laser uterosacral nerve ablation was compared with no surgical treatment. There was a statistically significant improvement in the treatment group compared with no treatment at 6 months (62.5% vs 22.6%), and this benefit was continued in more than 90% of patients for up to 1 year.[2] In an RCT by Abbott et al.[3] published in 2004, immediate laparoscopic excision was compared with delayed excision at 6 months, and patients were followed up for up to 12 months after the initial surgery. Statistically, more patients had improvement of pain after excision versus placebo (80% vs 32%) per the protocol. Both these trials compared a surgical technique (or combination of techniques) with no treatment (or delayed treatment), and the results of the techniques cannot be compared against each other.

There have only been 2 RCTs that directly compared ablation and excision in the laparoscopic management of endometriosis. A small trial of 24 women performed by

Wright et al.[4] in 2005 compared excision of endometriosis versus ablation and found that both treatments reduced overall symptom scores by roughly 30% at 6 months. However, given the small numbers, the study was underpowered, and no conclusions can be drawn from this trial. A second, more recent RCT performed by Healey et al.[5] in 2010 was powered to compare laparoscopic excision versus ablation of endometriosis for the primary outcome of pelvic pain. There was no statistically significant difference in improvement of pelvic pain using the visual analog scale (VAS) at 12 months when comparing excision versus ablation (56.4% vs 48.4%). However, there were trends in improvement for dyschezia and dyspareunia. An overall assessment of pain symptoms, such as quality of life (QOL), was not performed. The authors advised that these results are only applicable to results achievable by a generalist gynecologist and are not necessarily applicable to a specialist.

In practice, there is a tendency for gynecologic surgeons to want to perform ablation because it is considered easier. Theoretically, excision is advantageous because it ensures that the entire lesion or pathologic tissue is removed, especially for deeply infiltrating endometriosis or disease found over a vital organ or structure.

The purpose of this study was to collect data from several referral sites, both academic and private, with experience and expertise in treating endometriosis by excision. There were 2 specific aims for the study, meant to be used as a pilot feasibility study for a subsequent comparative RCT that might give new information on whether excision or ablation is the better technique for treating symptomatic endometriosis. First, we aimed to obtain an estimate of the proportion of symptomatic women being treated for endometriosis at surgical referral sites who would be willing to participate in a randomized trial of laparoscopic excision versus ablation of endometriosis. Second, we aimed to estimate the magnitude of change in pain symptoms and global QOL in symptomatic women at least 6 months after undergoing laparoscopic excision only of endometriosis at several different referral centers.

METHODS

Informed consent was obtained and documented for patients seen at 5 referral centers in North America (formerly Duke University Center for Endometriosis Research & Treatment in Durham, North Carolina [currently Saint Louis University Center for Endometriosis in St. Louis, Missouri]; Center for Endometriosis Care in Atlanta, Georgia; Northshore University Health System in Evanston, Illinois; Florida Hospital in Orlando, Florida; and Memorial University in St. John's, Newfoundland, Canada) that specialize in the management of pelvic pain or endometriosis. A 2-page (front and back) questionnaire was then administered by the site investigator and/or the nursing staff. The study was approved by the institutional review board at each of the institutions.

Questions from the survey included information on baseline demographics, severity and type of pain, previous medical and surgical history, and openness to participating in a randomized trial comparing excision versus ablation on the surgical management of endometriosis. The goal was to obtain information from approximately 20 consecutive patients per site, for a total of 100 patients. Data on the number of patients per site, as well as operative data, were collected. A follow-up 2-page questionnaire, sent by mail or administered by a phone consultation, was completed starting at 6 months after the surgery.

Inclusion criteria were female patients, aged 18 to 55 years, with endometriosis-associated persistent pelvic pain defined as all of the following: 3 months of chronic pelvic pain (defined as average pain intensity >5 of 10 for >50% of that time), which must have been predominantly localized to the pelvic region, bounded by the umbilicus superiorly and the inguinal ligament and symphysis pubis inferiorly, and could not be solely from the lumbar back or the skin (thus excluding isolated lumbago and vulvodynia); pain despite 1 class of medical treatments (eg, over-the-counter anti-inflammatories or hormonal suppression with oral contraceptives) for their endometriosis-associated pain; and at least 1 pelvic visceral pain component (dysmenorrhea, dyspareunia, dyschezia, or dysuria).

Exclusion criteria included prior bilateral salpingo-oophorectomy or post–natural menopause status, as well as significant mental or chronic systemic illness that might confound pain assessment or the ability to complete the study.

The primary symptom outcomes measured were QOL and pain—pelvic pain, dysmenorrhea, dyspareunia, and bowel and bladder symptoms. Analysis of variance and Fisher exact tests were used to compare the baseline demographic data between the centers as appropriate. VAS scores are a validated way to measure pain and were used to measure overall pelvic pain, as well as the different types of visceral pain.[6] Patients were asked on the preoperative and postoperative questionnaire to rate their pain by placing a mark on a 10-cm line, and the measured distance to the mark (in millimeters) gave the VAS score.

QOL was also assessed simply as an overall assessment of symptoms, before and after surgery, by asking the patient to rate it on a scale from 0 to 100. This way of measuring QOL has been validated in previous studies.[7] Paired *t* tests were used to compare VAS scores and QOL scores when a close-to-normal distribution could be assumed. When the numbers were smaller or a normal distribution could not be assumed, nonparametric tests were used as appropriate (eg, signed rank test or sign test).

Analysis of variance and Kruskal-Wallis (nonparametric) tests were used to compare the change in VAS scores and in QOL scores between the centers as appropriate. Fisher exact tests were used to compare the rate of histologically proven endometriosis by preoperative symptom between centers.

The other important outcome measured was the percentage of participants who would be willing to be randomized in a controlled study of excision versus ablation. This was reported simply as a percentage of those surveyed who responded yes to this question.

RESULTS

Consecutive patients seen at any of the 5 participating centers and who met the inclusion criteria were invited to be included in the study. There were a total of 100 patients (**Figure 1**) who enrolled in the study and completed the informed consent form, 90% (90 of 100) of whom underwent excision surgery. Of the 90 patients who underwent surgery, 72.2% (65 of 90) had histologically confirmed endometriosis and 61.1% (55 of 90) completed a postoperative questionnaire. The mean time after which the follow-up questionnaire was completed was 8.5 months (range, 6–14 months).

Of particular interest, 84.0% (84 of 100) of the patients who completed the initial questionnaire indicated that they would be willing to participate in a randomized trial of laparoscopic excision versus ablation of endometriosis.

There was no difference in the baseline demographics of the patients seen at the 5 centers (**Table 1**), except for previous medical therapy. Overall, more than 80% of patients presenting to the 5 centers had previous surgical interventions and more than 90% of patients had previous hormonal therapy. Of the patients in whom histologically proven endometriosis was found, 55 of 65 (84.6%) overall had received previous hormonal therapy or surgery.

When we compared VAS scores after surgery with those before surgery in the patients who had confirmed endo-

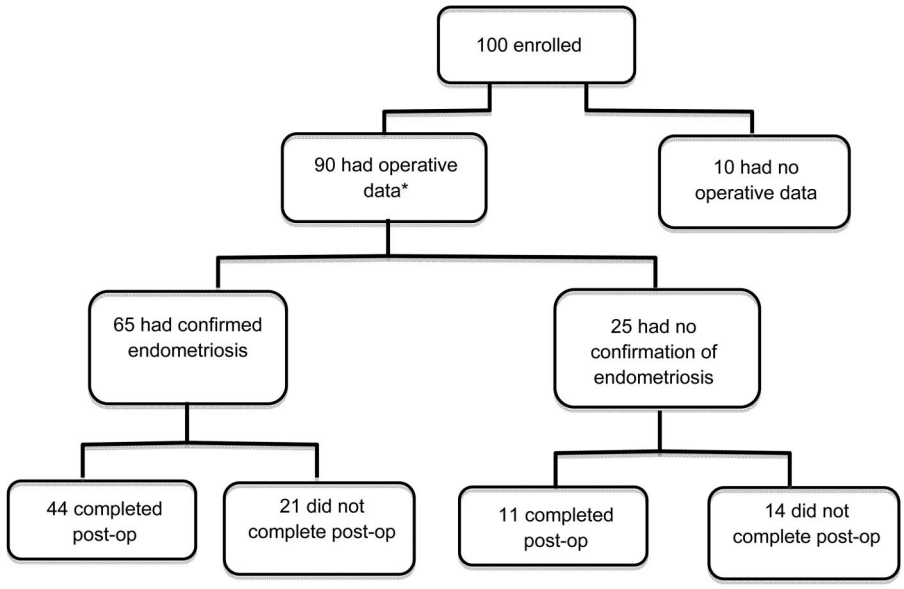

Figure 1. Flowchart of recruited subjects at all centers.
*The 90 patients who underwent surgery were distributed across the 5 centers as follows: 50 from Center for Endometriosis Research & Treatment, Duke University, Durham, North Carolina; 20 from Center for Endometriosis Care, Atlanta, Georgia; 11 from Northshore University Health System, Evanston, Illinois; 5 from Florida Hospital, Orlando, Florida; and 4 from Memorial University, St. John's, Newfoundland, Canada.

Table 1.
Baseline Demographics Overall and by Center

	Overall (100)	DU[a] (59)	CE[a] (20)	NS[a] (13)	MU[a] (4)	FH[a] (4)	*P* Value
Age at presentation (y)	31.6	31.1	32	32.3	34.3	32.8	.91
Age at menstruation (y)	12.3	12.4	12.2	12.6	11.8	11.8	.78
Duration of pelvic pain (y)	9.3	9	11.6	8.2	9	7.2	.64
White	85/100 (85%)	50/57 (88%)	17/20 (85%)	10/13 (77%)	3/4 (75%)	5/5 (100%)	.31
History of infertility	31/95 (32.6%)	17/58 (29.3%)	4/20 (20%)	6/13 (46.2%)	2/4 (50%)	2/5 (40%)	.44
Previous medical treatment	87/95 (91.6%)	53/58 (91.4%)	14/20 (70%)	13/13 (100%)	3/4 (75%)	4/5 (80%)	.04
Previous surgery	78/95 (82.1%)	45/58 (77.6%)	18/20 (90%)	11/13 (84.6%)	1/4 (25%)	3/5 (60%)	.05

[a]CE = Center for Endometriosis Care, Atlanta, GA; DU = Center for Endometriosis Research & Treatment, Duke University, Durham, NC; FH = Florida Hospital, Orlando, FL; MU = Memorial University, St. John's, Newfoundland, Canada; NS = Northshore University Health System, Evanston, IL.

metriosis, there was a significant reduction in pain scores for all symptoms except bowel symptoms (**Table 2**). Of the symptoms that had significant reductions in pain by VAS score, bladder pain showed the least (1.8 reduction) and dyspareunia showed the most (2.9 reduction). Also of note, the QOL scores were significantly improved after excision surgery, with a mean improvement of 19.5 points ($P < .001$). Comparisons were also made for the change in symptoms and QOL scores with hormonal suppression versus without hormonal suppression, and there were no significant changes found for any of these comparisons (**Table 2**). In addition, the change in VAS scores and the change in QOL scores were compared between the centers, and no significant differences were found. When looking at the patients who underwent surgery and who did not have histologically confirmed endometriosis, we found no improvement in QOL scores, although there was improvement in pelvic pain ($P < .01$) and dyspareunia ($P = .03$).

Pain symptoms (chronic pelvic pain, dysmenorrhea, dyspareunia, bowel symptoms, bladder symptoms) when present had a rate of histologically proven endometriosis ranging from 71.6% to 74%, with chronic pelvic pain being the least predictive and deep dyspareunia being the most predictive (**Table 3**). These results were compared between centers, and no significant differences were found.

DISCUSSION

A particular strength of this study is that it describes outcomes after excision for endometriosis from multiple referral centers; as such, it is the first study known to include data from multiple centers after excision. This shows that a multicenter trial is feasible, even among surgical referral sites. Most studies that have been published on excision for the surgical management of endometriosis have been from a single surgeon or center.[5,8,9]

Patients were suspected to have endometriosis based on the overall assessment of the surgeon from the clinical history and examination findings. One of the benefits of excision is the histologic confirmation of disease, and more than 7 of 10 patients who underwent surgery in this study for the suspicion of endometriosis had histologically proven disease. Even more noteworthy is that of the patients in whom histologically proven endometriosis was found, a high percentage (84.6%) had received either previous hormonal therapy or surgery by ablation as "treatment" for presumed endometriosis, indicating that these interventions are ineffective at suppressing or preventing disease. The data from this study further indicate that the addition of hormonal suppression after excision did not further reduce VAS scores for pain or benefit QOL scores, when compared with patients without postoperative hormonal suppression.

In the RCT of excision versus ablation for endometriosis by Healey et al.[5] (2010), differences in pelvic pain were not statistically significant, but there were trends for a difference in bowel-related symptoms and dyspareunia. In addition, as mentioned earlier, the results of their study came from a single center and are likely only applicable to generalist gynecologists. In our prospective multicenter study on excision for endometriosis, there were significant reductions in pelvic pain, dysmenorrhea, dyspareunia, and bladder symptoms but not bowel symptoms.

In contrast to the study by Healey et al.,[5] where fewer than one-third of patients who underwent surgery previously

Table 2.
VAS and QOL Scores Before and After Surgery in Patients Who Had Confirmed Endometriosis

	Preoperative	Postoperative	Change in Score	*P* Value
Pelvic pain	5.2 (n = 65)	2.4 (n = 43)	–2.6	< .001[a,b]
Postoperative suppression	5.3 (n = 23)	2.8 (n = 24)	–2.5	.19[c,d]
No suppression	4.6 (n = 39)	2.5 (n = 37)	–2.1	
Dysmenorrhea	7.5 (n = 65)	4.0 (n = 36)	–2.6	.002[a,e]
Postoperative suppression	7.5 (n = 23)	4.7 (n = 19)	–2.8	.32[b,c]
No suppression	7.1 (n = 38)	3.3 (n = 16)	–3.8	
Dyspareunia	5.1 (n = 61)	2.0 (n = 41)	–3.0	< .001[a,f]
Postoperative suppression	5.1 (n = 21)	3.0 (n = 22)	–2.1	.20[c,e]
No suppression	4.9 (n = 38)	1.0 (n = 18)	–3.9	
Bowel symptoms	3.4 (n = 65)	2.0 (n = 42)	–0.3	.6[a,b]
Postoperative suppression	3.8 (n = 23)	2.5 (n = 23)	–1.3	.22[c,e]
No suppression	3.1 (n = 37)	1.5 (n = 18)	–1.6	
Bladder symptoms	2.6 (n = 65)	0.6 (n = 41)	–1.8	< .001[a,e]
Postoperative suppression	2.5 (n = 23)	0.8 (n = 22)	–1.7	.11[c,g]
No suppression	2.5 (n = 37)	0.4 (n = 18)	–2.1	
QOL	63.3 (n = 65)	83.3 (n = 43)	20.0	< .001[a,e]
Postoperative suppression	60.8 (n = 23)	78.5 (n = 24)	17.7	.15[b,c]
No suppression	67.7 (n = 37)	89.3 (n = 18)	21.6	

[a]Comparison of preoperative and postoperative scores for symptom.

[b]*t* Test.

[c]Comparison of changes in system with and without hormonal suppression.

[d]Wilcoxon 2-sample test.

[e]Sign test.

[f]Signed rank test.

[g]*t* Test with Satterwaite correction for unequal variances.

Table 3.
The Rate of Histologically-Confirmed Endometriosis by Preoperative Symptom

Symptom	Overall	DU[a]	CE[a]	NS[a]	MU[a]	FH[a]
Pelvic pain	58/81 (71.6%)	35/45 (77.8%)	14/19 (73.9%)	6/9 (66.7%)	2/3 (66.7%)	(0/5) 0%
Menstrual cramps	61/83 (73.5%)	37/46 (80.4%)	14/17 (82.4%)	7/11 (63.6%)	3/4 (75%)	(0/5) 0%
Pain with intercourse	57/77 (74.0%)	37/44 (84.1%)	12/17 (70.6%)	6/9 (66.7%)	2/3 (66.7%)	(0/4) 0%
Pain with bowel movements	39/54 (72.2%)	21/25 (84%)	11/15 (73.3%)	6/10 (60.0%)	1/1 (100%)	(0/3) 0%
Pain with full bladder	32/44 (72.7%)	18/25 (72%)	9/14 (64.3%)	3/6 (50.0%)	2/2 (100%)	(0/2) 0%

[a]CE = Center for Endometriosis Care, Atlanta, GA; DU = Center for Endometriosis Research & Treatment, Duke University, Durham, NC; FH = Florida Hospital, Orlando, FL; MU = Memorial University, St. John's, Newfoundland, Canada; NS = Northshore University Health System, Evanston, IL.

received either hormonal or surgical treatment, patients in our study received either hormonal or surgical treatment in the vast majority of cases (>80%). One might predict that patients having previous treatment might respond with less benefit from another surgical intervention, yet the rates of improvement in VAS scores were comparable in both studies. Also of note is the finding that patients did not have symptom improvement in QOL scores when no endometriosis was found histologically.

A strength of this study is the inclusion of a single validated measure of QOL before and after excision surgery. A scale of 0 to 100 for the QOL score is easy to use and has been validated as an assessment tool.[7] Most studies on the surgical management of endometriosis use pelvic pain as the primary outcome as measured by VAS scores.[1,3,5] A potential problem with using pelvic pain as the primary outcome of a study on endometriosis is that some components of pain may improve after surgically treating endometriosis whereas others may not, at least to the same extent. A QOL assessment may be a better overall measure of the clinical benefit of surgery for treating endometriosis by translating multiple pain symptoms to a single measure of their effect on daily functioning. In fact, published reviews have recommended the inclusion of a QOL assessment in trials that look at pain as an outcome.[10,11] Our study showed a statistically significant improvement in QOL scores after excision at multiple centers. It is our recommendation that a QOL measure be used as the primary symptom outcome measure for future comparative trials on excision versus ablation in the surgical management of endometriosis. This study has produced an estimate of the benefit on QOL after excision to be an increase of 20 points. There are no known studies that have evaluated QOL after ablation.

Weaknesses of this study include the skewed actual numbers of recruitment, with more than 58 of 100 patients coming from a single center and 78 of 100 from 2 centers. Perhaps more important is the lack of quality assurance or some objective way to determine whether adequate or complete excision of all areas of abnormal peritoneum was achieved at each of the centers. In any subsequent randomized comparative trial comparing excision and ablation, objective or third-party quality assurance will need to be included for both techniques, especially if a particular referral center favors a particular approach over the other.

As reported in a recent study on complete excision of endometriosis in teenagers, one of the most important benefits of excision may not be symptom relief but may be eradication of disease.[12] Potential eradication of disease by excision might benefit future fertility, and this benefit might need to be evaluated also in a comparative trial of excision versus ablation in the treatment of endometriosis.

One of the aims of this study was to obtain an estimate of the rate of patients presenting to referral centers for pelvic pain or endometriosis (in particular, centers that specialize in the excision of endometriosis) who would be willing to be randomized to either excision or ablation of endometriosis at the time of surgery. The vast majority of patients (84.0%) were willing to be randomized when asked this question. This bodes well for the feasibility of a randomized comparative trial even at referral centers that specialize in a particular surgical approach to the treatment of endometriosis.

The results of this study indicate that patients were overwhelmingly willing to be randomized to either excision or ablation for endometriosis even at referral centers, that QOL may be a better overall measure as a primary outcome when one is looking at the benefit of surgery for endometriosis, and that a comparative RCT is feasible, as well as needed, among multiple centers that specialize in surgically treating endometriosis.

CONCLUSION

A multicenter prospective study evaluating surgical treatment for endometriosis is feasible. Another comparative trial comparing excision versus ablation in the surgical management of endometriosis is needed at multiple centers but also with primary outcomes other than simply pelvic pain. Patients are willing to be randomized even at referral centers that treat endometriosis.

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