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Review Article

Identifying the Problems of Randomized Controlled Trials for the Surgical Management of Endometriosis-associated Pelvic Pain

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ABSTRACT **Objective:** To report on randomized controlled trials (RCTs) that examine the surgical treatment of endometriosis-associated pelvic pain and to highlight their strengths and weaknesses.

Data Sources: We performed a systematic review of English-language, full-text articles addressing the surgical management of pain symptoms associated with endometriosis. The terms *endometriosis*, *pain*, *surgery*, *laparoscopy*, *plasma*, and *laser* were used for searches in Cochrane, MEDLINE, EMBASE, and clinical trial databases. Additional studies were identified from references in electronically located articles.

Methods of Study Selection: A literature search was conducted by 2 authors, and abstracts were independently screened for inclusion, with the resolution of any discrepancy by a third author. Randomized studies that reported pain before and after surgery were eligible for inclusion. Supporting data from nonrandomized trials were used for discussion. The Cochrane risk-of-bias assessment was performed on included studies.

Tabulation, Integration, and Results: Search results for available articles from 1996 to October 2019 revealed 594 potential studies, with 20 studies meeting the final inclusion criteria. Comparative studies of surgery vs no surgery for an effect on pain, surgical approach, the effect of different locations of disease on pain, nerve-dividing techniques for pain, and nerve-sparing effects for pain were studied. RCTs reported a substantial reduction in pain compared with no surgery in up to 80% of women; however, up to a third of women in these studies reported a placebo response. There was no evidence of a difference in pain reduction with the mode of surgery (laparoscopy, laparotomy, or robot-assisted laparoscopy). There is limited evidence stating that excision is superior to ablative surgery; however, there are confounders in the reporting of disease location and depth and the pain symptoms most affected. We need to reconsider the hypothesis that disc excision results in fewer complications and has superior outcomes to those of segmental resection in light of the first RCT on this subject. Nerve-dividing surgery for pain has been demonstrated to be of no value for uterosacral nerve ablation and/or division and of limited (if any) value for presacral neurectomy.

Conclusion: Although surgical RCTs have always been difficult to undertake, there are 16 RCTs on endometriosis-associated pain. Ethical considerations, the equipoise of surgeons and participants, and follow-up duration are important parameters in establishing RCTs. In addition, we must be willing to accept and adopt the evidence when it does demonstrate a particular outcome, such as the fact that surgical uterosacral nerve disruption does not improve pain or that disc excision does not substantially reduce complications compared with segmental resection for bowel disease, as suggested by previous nonrandomized studies. If we accept that a well-conducted RCT provides best-quality evidence, then we should at least be open to the possibility that our long-held views may be challenged and changed with new science in our practice. Journal of Minimally Invasive Gynecology (2019) 00, 1−14. © 2019 AAGL. All rights reserved.

Keywords: Endometriosis and pain; Surgical treatment; Randomized controlled trial

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Scientific studies demonstrate that multiple mechanisms underlie endometriosis-associated pain, including local nociception, local inflammation, systemic inflammation, and alterations in peripheral and central nervous system pain processing [1−3]. Most endometriosis disease staging systems do not account for pain severity [1,4] and likely reflect the complex pathogenesis of endometriosis, which includes the overexpression of nerve growth factor [5] in peritoneal fluid and changes in neural structure that may potentiate the disease [6]. Although surgical removal of the disease may reduce symptoms, the recurrence of pain both with and without evidence of recurrent disease is a recognized sequelae [7,8].

Endometriosis management using progestins or estroprogestins relieves pain symptoms in more than 90% of women at 1 year [9]; however, medical therapy fails in approximately 30% of women [7]. In these cases, surgical treatment of endometriosis lesions has been demonstrated to alter inflammatory profiles both locally and systemically and to reduce pain symptoms [3,10−12].

Surgical approaches including laparotomy, laparoscopy, and robotic-assisted laparoscopy are used to access the pelvis for endometriosis surgery [13], and a variety of techniques and tools to treat the disease at various locations have been described. This review aims to identify randomized controlled trials (RCTs) that study the surgical treatment of endometriosis-associated pain and highlight their strengths and weaknesses. The use of medical therapies in conjunction with surgery and hysterectomy variants has not been addressed in this review.

Materials and Methods

A literature search was conducted by 2 authors, and abstracts were independently screened for inclusion, with any discrepancy resolved by the third author. A search was conducted in the Cochrane, MEDLINE, and EMBASE databases from 1996 to October 2019 using the terms *endometriosis*, *pain*, *surgery*, *laparoscopy*, *plasma*, and *laser*. The terms *surgery* OR *laparoscopy* OR *plasma* OR *laser* were combined with *endometriosis* AND *pain*. In addition, the Australia and New Zealand Clinical Trial registry (www.anzctr.org.au), United States Clinical Trials registry (https://clinicaltrials.gov), and European Clinical Trials registry (https://www.cinicaltrialsregister.eu) were searched for current trials on this topic using the terms *endometriosis*, *pain*, *laparoscopy*.

When a conference abstract was identified in the search but not in a corresponding published article, the abstract author was contacted for complete data. Systematic reviews were screened for additional RCTs not previously identified. Included articles were hand-searched to identify studies from other sources that may not have been otherwise identified.

Articles in which the full text was published in English, a randomized trial was undertaken for the treatment of pain in women with endometriosis, a surgical intervention and surgical comparator were reported, pain measures were specified, and change of pain symptoms from baseline was reported were included. Articles describing a surgical technique but not symptoms were excluded, as were those including hysterectomy variants. The review has been submitted to the International Prospective Register of Systematic Reviews (Registration number CRD42019133450).

The Cochrane risk-of-bias tool [14] was used by 2 authors, with disagreements settled by a third author. Where appropriate, outcome data were synthesized when 2 or more RCTs reported the same intervention and comparator with a similar time to follow-up and the use of the same pain scale. The change in pain score was the only datum synthesized and could have been presented as the mean reduction in pain scores, a percentage of pain reduction, or a risk ratio between the intervention and the comparator. Risk ratios for individual studies were combined using a random-effect meta-analysis and were assessed for heterogeneity.

When studies could not be combined, they were reported collectively on the basis of the intervention and comparator. Identified RCTs that examined specific surgical interventions and comparators were included in the analysis. This probably included surgery compared with placebo or different types of surgical techniques. The results were grouped according to categories for ease of reference, including (1) placebo-controlled surgical trials for pain, (2) the mode of surgical approach for pain, (3) the outcome of surgical techniques for pain, and (4) the use of denervation surgery for pain.

Results

The search results are presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram in Fig. 1. Sixteen original RCTs were included, with 4 articles with long-term follow-up. Table 1 summarizes the risk of bias of the included RCTs.

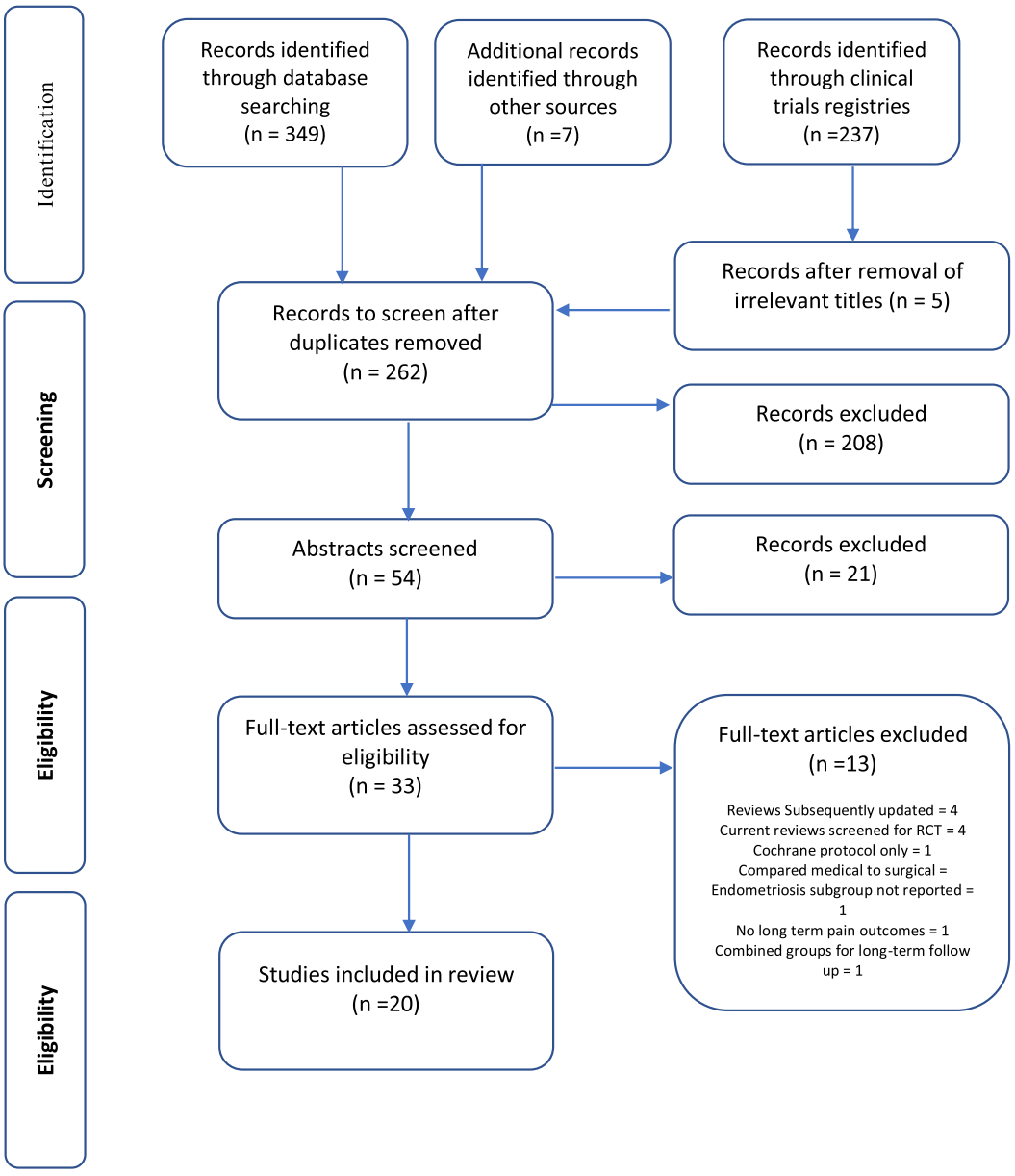
The 16 RCTs included 1245 women who participated in areas set out in the Materials and Methods. Table 2 summarizes the results of the included trials, categorized by intervention. Specific results separated by these categories are set out in the following sections.

Does Surgery to Reduce Endometriosis-associated Pain Work?

Three surgical RCTs including 131 participants compared diagnostic (the placebo arm) and operative laparoscopy for pain symptoms from baseline to 6 or 12 months after index surgery [7,8,15], with the extended follow-up of 1 trial reported separately [16]. Table 2 details the outcomes of these RCTs, with 62.5% to 80% of women undergoing laser vaporization or surgical excision and reporting relief or reduction in pain symptoms at 6 months after surgery. Many participants had undergone previous medical treatments, but few participants had undergone previous

Fig. 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram.



surgery, resulting in these studies principally examining the effect of the first surgery for pain. All of these RCTs report a notable, reproducible, and typical placebo effect, with up to a third of women with demonstrable endometriosis randomized to placebo surgery (diagnostic laparoscopy) reporting a reduction in pain symptoms compared with those at baseline [7,8,15,16]. In addition, these RCTs demonstrate that despite the surgical excision of disease, it may recur at the same area or in different areas in the pelvis within 6 to 12 months of the index procedure, although the follow-up duration and power are insufficient to understand the implication of recurrence on symptom response or final disposition.

In 1 of these studies [15], follow-up was poor with only 16 of 29 (55%) being followed up until the end of the defined study duration. Overall, although these RCTs have a low risk of bias, they are all underpowered to note the specific effect of surgical removal of superficial disease compared with deep disease or ovarian endometriomata, with only 1 of the 3 RCTs including women with extensive (revised American Society for Reproductive Medicine stage IV) disease (a total of 17/131 participants [13%]). In 1 of the RCTs, 9 of 29 women (31%) did not have a histologic diagnosis of endometriosis, and this further limits its external validity because, in that case, this is not a study purely on endometriosis-associated pain.

Table 1

Risk of bias of included studies

Author, yr	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall risk-of-bias assessment
Abbott et al, 2004 [8]	Low	Low	Low	Low	Low	Low	Low
Alborzi et al, 2004 [27]	Low	Some concerns	Low	Some concerns	Low	Low	Some concerns
Beretta et al, 1998 [26]	Low	Some concerns	Unclear	Some concerns	Low	Low	Some concerns
Daraï et al, 2010 [18]	Low	Some concerns	Some concerns	Some concerns	Low	Low	Some concerns
Healey et al, 2010 [23]	Low	Low	Low	Low	Low	Low	Low
Roman et al, 2017 [33]	Low	Low	Some concerns	Some concerns	Low	Low	Low
Jarrel et al, 2005 [15]	Low	Low	Some concerns	Low	High risk	Some concerns	Some concerns
Johnson et al, 2004 [38]	Low	Low	Low	Low	Low	Low	Low
Riley et al, 2019 [24]	Low	Low	Low	Low	High risk	Some concerns	Low
Seracchioli et al, 2014 [29]	Low	Low	Low	Low	Low	Low	Low
Soto et al, 2017 [17]	Low	Some concerns	Some concerns	Some concerns	Some concerns	Low	Some concerns
Sutton et al, 1994 [7]	Low	Some concerns	Low	Low	Some concerns	Some concerns	Some concerns
Sutton et al, 2001 [37]	Low	Low	Low	Low	Low	Low	Low
Vercellini et al, 2003 [36]	Low	Low	Some concerns	Some concerns	Low	Low	Low
Wright et al, 2005 [22]	Low	Some concerns	Some concerns	Some concerns	Low	Low	Low
Zullo et al, 2003 [35]	Low	Low	Low	Low	Low	Low	Low

Table 2

Summary of RCTs examining the role of surgery in reducing reduce endometriosis-associated pain

Record	Participants	Intervention	Comparator	Pain measure	Length of follow-up	Results	Comments
Placebo-controlled surgical trials							
Jarrel et al, 2005 [15]	29 women with severe pelvic pain - 15 excision - 14 control	Complete excision of visible disease	Biopsy to confirm disease only (control group)	Aggregate of daily VAS score of the chest, back, abdomen, pelvic, and thigh pain over 1 mo	11 to 12 mo (15 women remain)	Reduction in aggregate VAS score at 12 mo - 45% vs 33% - ns	r-ASRM stage I to III disease Postsurgical medical therapy not described
Abbott et al, 2004 [8]	39 women with clinical signs and symptoms of endometriosis - 20 immediate excisions - 19 delayed excisions	Complete excision of endometriosis at index surgery. Re-excision at surgery 2 (6 mo), if present	Expectant management Excision at surgery 2 (6 mo)	Aggregate VAS for dysmenorrhea, nonmenstrual pelvic pain, dyspareunia, and dyschezia	Before second surgery at 6 mo 12 mo from first surgery	Reduction in aggregate VAS: 30 of 100 vs 0 of 100; p = .012 Proportion of women reporting improved pain: 80% vs 32%; p = .002 Reduction in aggregate VAS: 50 of 100 vs 82.5 of 100; p = ns Proportion of women with improve pain: 53% vs 83%; p = ns	All stages of disease 9 or 16 (57%) of the immediate group had no disease at 6 mo. Overall 88% had improvement in disease score.
Sutton et al, 1994 [7]	63 women with pain suggestive of endometriosis - 32 laser - 31 expectant	Laser ablation + uterine nerve transection	Expectant management	Pain intensity measured on a 10-cm linear scale	6 mo	Median reduction in linear scale for pain: 2.85 vs 0.05 cm; p <.01 Proportion of women reporting improved pain: 62.5% vs 22.6%; p <.01	r-ASRM stage I to III disease Surgery offered to the expectant group at 6 mo Excluded from trial if using hormonal suppression
Sutton et al, 1997 [16]	12 mo follow-up of 63 women after immediate laser ablation or delayed surgery for endometriosis	Laser ablation + uterine nerve transection at index surgery	Laser surgery at second surgery, 6 mo after index surgery	Pain intensity measured on a 10 cm linear scale	12 mo	Proportion of women expectant group reporting improved pain compared with that at baseline: 71% vs 29%; p value not reported Proportion of intervention group reporting increased pain since the 6-mo review: 10%	

Table 2

Continued

Record	Participants	Intervention	Comparator	Pain measure	Length of follow-up	Results	Comments
Surgical approach trials							
Soto et al, 2017 [17]	73 women with pelvic pain - 35 robotic group - 38 laparoscopic group	Robot-assisted laparoscopy	Conventional laparoscopy	EHP-30 for pain	6 mo	Change in EHP-30 score for pain: 26.4 vs 32.7; p = ns	No difference in r-ASRM stage
Daraï et al, 2010 [18]	52 women with colorectal endometriosis requiring colorectal resection - 26 laparoscopic - 26 open surgery	Laparoscopic segmental bowel resection	Open segmental bowel resection	VAS for dysmenorrhea, dyspareunia, and dyschezia	19 mo (median)	Mean reduction in VAS Dysmenorrhea: 5 vs 5.5; p = ns Dyspareunia: 4.3 vs 3.8; p = ns Dyschezia: 3.4 vs 3.3; p = ns	Concurrent ovarian cystectomy, salpingo-oophorectomy, hysterectomy, and uterosacral ligament resection was performed as necessary
Touboul et al, 2015 [19]	40 women with colorectal endometriosis requiring colorectal resection - 20 laparoscopic group - 20 open surgery group	Laparoscopic segmental bowel resection	Open segmental bowel resection	VAS for dysmenorrhea, dyspareunia, dyschezia, and dysuria	51 mo	Mean reduction in VAS Dysmenorrhea: 2.3 vs 22; p = ns Dyspareunia: 2.2 vs 2.2; p = ns Dyschezia: 1.0 vs 2.0; p = ns Dysuria: 1.9 vs 2.4; p = ns	Concurrent ovarian cystectomy, salpingo-oophorectomy, hysterectomy, and uterosacral ligament resection was performed as necessary
Surgical technique trials							
Riley et al, 2019 [24]	73 women with chronic pelvic pain or known endometriosis - 37 excision group - 36 ablation group	Excision of disease	Ablation of disease	VAS for dysmenorrhea, nonmenstrual pelvic pain, dyspareunia, and dyschezia	12 mo	Mean reduction in VAS Dysmenorrhea: 24.15 vs 14.8; p = ns Nonmenstrual pain: 10.41 vs 9.46; p = ns Dyspareunia: 9.4 vs 2.66; p = ns Dyschezia: 7.7 vs 2.73; p = ns	Women with deep disease excluded No difference between groups of women using hormonal therapy
Healey et al, 2010 [23]	178 women with symptoms of endometriosis - 89 excision - 89 ablation	Excision of disease	Ablation of disease	VAS for pain on a 10 cm line	12 mo - 49 women in excision group - 54 women in ablation group	Mean reduction in VAS for overall pain: 3.1 vs 3.0; p = ns	Significantly higher r-ASRM scores in the excision group (10 vs 7; p = .014) and more deep disease in the excision group (28 of 54 [53%] vs 11 of 49 [22%]; p = .002) Study underpowered second to drop-out rate

Table 2

Continued

Record	Participants	Intervention	Comparator	Pain measure	Length of follow-up	Results	Comments
Healey et al, 2014 [25]	5-yr follow-up after excision vs ablation of endometriosis	Excision of disease	Ablation of disease	VAS for pain on a 10 cm line	5 yrs after index surgery: 40 women in the excision group 42 women in ablation group	Mean reduction in VAS for overall pain: 5.8 vs 5.5; p = ns Mean reduction in VAS for abdominal pain: 3.2 vs 4.8; p = .03 Mean reduction in VAS for dyspareunia: 6.0 vs 3.2; p = .007	Multivariate analysis conducted to allow for medication used to treat endometriosis, age, r-ASRM stage, and DIE.
Wright et al, 2005 [22]	24 women with symptoms of endometriosis - 12 excision - 12 ablation	Excision of disease	Ablation of disease	Ranked ordinal scale of 1 to 5 for pain during palpation	6 mo	Mean reduction in score Dysmenorrhea: 0.7 vs 0.4; p = .42 Exercise pain: 0.36 vs 0.059; p = .63	
Surgical management of endometrioma trials							
Seracchioli et al, 2014 [29]	88 women with evidence of ovarian and posterior DIE - 44 ovarian suspension - 44 conservative surgery	Resection of endometriosis followed by ovarian suspension	Resection of endometriosis only	VAS for dysmenorrhea, chronic pelvic pain, dyspareunia, dyschezia, and dysuria	6 mo	Mean VAS reduction Dysmenorrhea: 6.3 vs 5.8; p = .97 Chronic pelvic pain: 3.6 vs 3.5; p = .96 Dyspareunia: 5.5 vs 4; p = .01 Dyschezia: 4.2 vs 3; p = .096 Dysuria: 1.8 vs 1.3; p = .286	Improved mobility of ovaries on ultrasound at 6 mo in the suspension group
Alborzi et al, 2004 [27]	100 women with endometriomas and either infertility or pelvic pain - 52 cystectomy - 48 fenestration and coagulation	Cystectomy of endometrioma	Fenestration of endometrioma and coagulation of lining	10-cm linear analog scale Reported only recurrence of symptoms	24 mo	Recurrence of symptoms: 15.8% vs 56.7%; p = .001	Pain scale values not reported Difference in pain scale before surgery and that at follow-up time points not reported
Beretta et al, 1998 [26]	64 women with advanced stages of endometriosis - 32 cystectomy - 32 fenestration and coagulation	Cystectomy of endometrioma	Fenestration of endometrioma and coagulation of lining	10-cm linear analog scale for dysmenorrhea, nonmenstrual pelvic pain, and deep dyspareunia Reported only recurrence of symptoms	24 mo	Recurrence rate of symptoms: Dysmenorrhea: 15.8% vs 52.9%; p <.05 Deep dyspareunia: 20% vs 75%; p <.05 Nonmenstrual pelvic pain: 10% vs 52.9%; p <.05	Pain scale values not reported Difference in pain scale before surgery and that at follow-up time points not reported

Table 2

Continued

Record	Participants	Intervention	Comparator	Pain measure	Length of follow-up	Results	Comments
Surgical management of endometriosis involving the bowel trials							
Horace et al, 2018	60 women with DIE of the rectum of more than 20 mm size - 27 conservative - 33 segmental resection	Conservative removal of lesion (rectal shaving or disc excision)	Segmental bowel resection	VAS for dysmenorrhea, dyspareunia, and intermenstrual pain	24 mo	Mean VAS scores at 24 mo Dysmenorrhea: 3 vs 4; p = .84 Dyspareunia: 4 vs 4; p = 1.00 Intermenstrual pain: 4 vs 4; p = .83	Shaving was performed by scissors, ultrasound scalpel, or plasma energy
Surgical denervation trials							
Zullo et al, 2003 [35]	126 women with dysmenorrhea caused by endometriosis - 63 PSN - 63 conservative surgery	Ablation or excision of endometriosis + PSN	Ablation or excision of endometriosis	100 mm VAS for dysmenorrhea Results report cure rate (absence or dysmenorrhea or that not requiring medical treatment)	12 mo	Cure rate of dysmenorrhea All disease: 85.7% vs 57.1%; p <.05 Stage I: 87.5% vs 61.1%; p = ns Stage II: 86.4% vs 57.1%; p = ns Stage III: 88.2% vs 58.8%; p = ns Stage IV: 75% vs 42.9%; p <.05 Deep rectovaginal septum disease: 57.1% vs 16.7%; p <.05	Women with previous pelvic surgery were excluded
Zullo et al, 2004 [34]	Two-yr follow-up of 120 women after PSN vs of those after conservative surgery	Ablation or excision of endometriosis + PSN	Ablation or excision of endometriosis	100-mm VAS for dysmenorrhea Results report cure rate (absence or dysmenorrhea or that not requiring medical treatment)	24 mo	Cure rate of dysmenorrhea All disease: 83.3% vs 53.3%; p <.05 Stage I: 87.5% vs 55.6%; p <.05 Stage II: 76.2% vs 52.4%; p <.05 Stage III: 75% vs 53.3%; p <.05 Stage IV: 71.4% vs 50%; p <.05	11 of 60 (18.3%) vs 0 of 60 (0%) developed long-term complications including bowel and urinary dysfunction after PSN

Table 2

Continued

Record	Participants	Intervention	Comparator	Pain measure	Length of follow-up	Results	Comments
Johnson et al, 2004 [38]	67 women with chronic pelvic pain and endometriosis - 32 uterine nerve ablation - 35 conservative surgery	Ablation or excision of endometriosis + uterine nerve ablation	Ablation or excision of endometriosis alone	10-point VAS for nonmenstrual pain, dysmenorrhea, deep dyspareunia, and dyschezia Results on the basis of ≥ 50% VAS reduction	12 mo	Proportion of women with ≥ 50% reduction in VAS Nonmenstrual pelvic pain: 11 of 22 (50%) vs 15 of 30 (50%); p = 1.00 Dysmenorrhea: 7 of 21 (33%) vs 11 of 24 (46%); p = .583 Dyspareunia: 6 of 10 (60%) vs 8 of 16 (50%); p = .701 Dyschezia: 7 of 14 (50%) vs 10 of 23 (43%); p = .699	All r-ASRM stages No pouch of Douglas obliteration in any patient Number of women required for power calculations not met
Vercellini et al, 2003 [36]	156 with symptoms of endometriosis - 78 uterosacral ligament resection - 78 conservative surgery	Ablation or excision of endometriosis + uterosacral ligament resection	Ablation or excision of endometriosis alone	VAS for dysmenorrhea, deep dyspareunia, and nonmenstrual pelvic pain	12 mo	Median VAS reduction Dysmenorrhea: 52 vs 59; p = ns Dyspareunia: 43 vs 33; p = ns Nonmenstrual pain: 32 vs 31; p = ns	
Sutton et al, 2001 [37]	51 women with pelvic pain and endometriosis - 27 uterine nerve ablation - 24 laser vaporization alone	Laser vaporization of endometriosis + uterine nerve ablation	Laser vaporization of endometriosis alone	10-point linear analog scale for dysmenorrhea, dyspareunia, and nonmenstrual pelvic pain	6 mo	Median pain score reduction Number of reports significant difference favoring conservative surgery for dysmenorrhea (p = .022) and nonmenstrual pelvic pain (p = .032)	r-ASRM stage I to III disease No pain score data provided to compare between groups

DIE = deep infiltrating endometriosis; EHP-30, endometriosis Health Profile 30; ns = no significant difference; PSN = presacral neurectomy; r-ASRM = revised American Society for Reproductive Medicine; VAS = visual analogue scale.

Does the Approach to Surgery Matter for Pain Outcomes?

We identified 2 RCTs comparing surgical approach and reporting comparative pain outcomes after the index surgery. In the first RCT, 73 women were assigned to robot-assisted or conventional laparoscopy [17] for superficial endometriosis with no differences at 6 months after operation identified in any aspect of the Endometriosis Health Profile 30, including pain. In the second RCT, 52 women were assigned to laparoscopic bowel resection vs open resection with no differences in the visual analogue scale (VAS) score for dysmenorrhea, dyspareunia, or dyschezia either at 19 months [18] or at the at 51-month follow-up [19].

Similar to nonrandomized comparison trials [12,20,21], limiting the stage of disease included or the location of disease limits the external validity of these studies. However, none of the studies show a difference in general or specific pelvic pain symptoms at follow-up.

Does the Surgical Technique for Disease Treatment Affect Pain Outcomes?

Excision Vs Ablation

We identified 3 RCTs randomizing 375 women and assessing pain scores for those undergoing excision compared with those undergoing ablation at 6 or 12 months from the index surgery [22−24] with follow-up to 5 years for 1 RCT [25]. There were no differences in dysmenorrhea at 12 months, although both short- and long-term follow-up up to 5 years [25] suggest an improvement in dyspareunia when excisional surgery was performed rather than ablation.

Cystectomy Vs Fenestration and Ablation for Endometriomata

The 2 RCTs involving 164 women [26,27] undergoing excision vs ablation techniques for endometrioma were subjected to a Cochrane review [28], with no new published RCTs in more than 14 years. These RCTs report the excision of an endometrioma being associated with reduced dysmenorrhea, dyspareunia, and nonmenstrual pelvic pain compared with the stripping of the endometrioma. A third study [29] randomized 88 women to either surgery alone or surgery and ovarian suspension to examine the effect of postsurgical adhesions on pain reduction. At 6 months after surgery, there were no differences between the groups in dysmenorrhea, chronic pelvic pain, dyschezia, or dysuria; however, there was reduced dyspareunia in the suspension group. Three RCTs have been identified in clinical trial registries related to the treatment of endometriomas; however, pain is not an outcome in these studies [30−32].

Surgery Involving Endometriosis on the Bowel

We identified a single RCT on deep infiltrating endometriosis of the rectum randomized for treatment by disc excision or shaving or segmental resection. Sixty women with deep infiltrating endometriosis of the rectum at up to 15 cm from the anal verge, measuring more than 20 mm in length and involving at least the muscularis layer in depth and 50% of the rectal circumference, were included [33], with no difference in VAS scores or quality-of-life questionnaire results. Both groups had equal rates of functional problems 24 months after surgery, including constipation, frequent bowel movements, defecation pain, anal incontinence, dysuria, and bladder atony, although segmental resection was associated with an increased risk of bowel stenosis.

Benefits of Other Surgery

Presacral Neurectomy and Uterine Nerve Ablation

A single RCT involving 125 women assessed the value of presacral neurectomy (PSN) and was subsequently reported in a long-term follow-up study [34,35]. Although improvement in pelvic pain symptoms, particularly dysmenorrhea, was achieved for all women, those who underwent PSN reportedly had a greater reduction in dysmenorrhea.

We identified 3 RCTs investigating the effect of laparoscopic uterosacral nerve ablation (LUNA) [36−38] involving 274 women. The earliest identified and smallest RCT [37] reported an improvement in the median pain scores for dysmenorrhea ($p = .022$) and nonmenstrual pain ($p = .032$) when LUNA was added to standard surgery. However, this small study excluded women with revised American Society for Reproductive Medicine stage IV disease, and pain scores were not provided. Subsequent larger and more robust studies [36,38] arrived at an opposing conclusion: no difference in the median VAS scores for dysmenorrhea, dyspareunia, or nonmenstrual pelvic pain at 12 months when LUNA was added to standard surgery.

Discussion

Placebo-controlled trials are lauded as the cornerstone of evidence-based medicine, and endometriosis is one of the first diseases to have not 1 but 3 controlled surgical RCTs comparing diagnostic (the placebo arm) and operative laparoscopy for the symptom of pain [7,8,15]. Although these trials demonstrate a benefit in most women, they highlight the placebo effect of diagnostic laparoscopy alone. Furthermore, these trials report that endometriosis may regress spontaneously when an observational, and not surgical, course is undertaken, particularly in small-volume peritoneal diseases. It is therefore important to consider that both the placebo effect and/or the natural course of an individual's disease process may contribute to the reduction in symptoms because of regression and that symptom reduction may not be a direct result of the surgery itself.

A Cochrane systematic review [39] and meta-analysis has reported that there is moderate-quality evidence that

surgery is useful in reducing pain compared with placebo for mild-to-moderate disease. The inclusion of participants with minimal disease is quite different in these studies, with this group accounting for 1 of 39 (2.5%) [8], 6 of 29 (21%) [15], and 29 of 63 (46%) participants [7], with severe disease present in 0% [7,15] and 44% (17 of 39) [8] of women, respectively. The question remains whether such heterogeneity in disease severity impacts outcome when both these RCTs and data from other non-RCTs regarding pain suggest that the severity of disease is not correlated with the severity of symptoms [40,41]. It is therefore difficult to be dogmatic about disease extent and to restrict surgical intervention on the basis of this particular parameter.

The early termination of the study by Jarrel et al [15] may have resulted from the publication of previous RCTs and the recommendation by the local Canadian health service that laparoscopic surgery is the standard of care for women presenting with pain. Such policy poses a considerable problem for any future RCTs comparing surgery with a no-surgery arm and may in part explain the approximately 15-year gap since the publication of the last controlled surgical trial comparing intervention with no intervention. It must be recognized that the total number of women randomized to all studies is small; the proportion of women with superficial-to-extensive deep disease is variable; and the short time frame with only 12-month follow-up for a chronic disease that may be present for more than 30 years of a woman's life. However, because of the results of these trials, it is (almost) untenable to consider a study that would randomize women to diagnostic or operative surgery and keep the participants blinded indefinitely. So, the durability of these initial results indicating that there is pain reduction for endometriosis by surgical treatment need that have been assessed by longitudinal data that support pain reduction over time [8,16]. Although there continue to be considerable debate over the efficacy of surgical treatment for endometriosis, the arguments stop at debate, with a lack of action regarding the considerable efforts on an ethics application and recruitment for such a study. The current weight of evidence would suggest that superficial disease needs to be included because this is the group that has the most variable outcome, but deep disease must be assessed, as there are only 17 women randomized to this severe group to a gold-standard study. We are aware of the initiation of a study recruiting women with mild disease to an RCT in the United Kingdom (personal communication) that may answer 1 of these questions. Until such times, the weight of evidence is in favor of the first surgical procedure having substantial impact to decrease pain among women with endometriosis.

Although a number of studies comparing surgical techniques for the completeness of resection, recurrence of disease, or cost analysis exist, we identified only 2 RCTs comparing surgical approach and reporting comparative pain outcomes after the index surgery. When the subgroups of minimally invasive approaches are compared, there are unsurprisingly no differences in the outcomes for patients, with pain outcomes of single-site laparoscopy being similar to convention laparoscopy [42] and those of conventional laparoscopy being similar to robot-assisted laparoscopy [17]. Although these studies make some statements regarding differences in the length of stay or cosmesis, the primary issue is that there is no biologic plausibility to suggest that pain outcomes would be different with any approach to surgery as long as the lesions are removed in full; it is this focus that should be the primary driver for undertaking the procedure. Therefore, the surgical approach is entirely dependent on the skill set of the surgeon and the availability of equipment. Future studies should keep in mind that clinically irrelevant findings that do not change the primary outcome for the patient are of limited value in this regard. Meaningful comparisons regarding clinical parameters or cost and healthcare system outcomes are appropriate; however, the avoidance of RCTs as marketing exercises is important.

The excision of disease vs ablation has long been controversial; however, the underlying premise of disease removal must be paramount, and the method must reflect the capacity to do so. When such studies are performed by expert excisional surgeons who may correctly identify both the presence of disease and extent, it is likely that lesions will be completely removed. It is imperative that for surgeons who undertake the ablative approach but do not perform excisional surgery that all lesions are removed and that an adequate assessment of the depth of disease is made at the time of surgery. The underestimation of the depth of disease and a failure to excise both glandular material and fibrosis [43] are likely to be factors associated with the failure of response to the index surgery and with the poorer response for pain symptoms such as dyspareunia where fibrotic changes around the uterosacral ligaments and cul de sac may contribute to nociception during intercourse.

Deep infiltrating disease that extends beyond the peritoneum into structures such as the uterosacral ligaments and that may involve organs such as the bowel, bladder, and ureter is common in women with endometriosis and nerve infiltration, and the direct inflammatory effect is a proposed additional contributor to pain [44]. We did not find any RCTs on this subject; however, small prospective studies [45−48] have identified that the complete removal of deep posterior compartment disease improves VAS pain scores not only for deep dyspareunia but also for other pelvic pain symptoms at the follow-up of 12 months. Large-scale retrospective studies that report on thousands of women and include disease removal from the pararectal space and the anterior compartment including partial cystectomy corroborate these findings at a follow-up to 2 years, although the selection bias that accompanies such methodology must always be recognized [11,49,50]. There is a reasonable volume of variable quality data that indicates that there is considerable improvement in the median pain scores for dysmenorrhea, deep dyspareunia, dyschezia, lower urinary tract symptoms during menstruation, and noncyclic chronic pelvic pain when deep disease is removed, with pain symptoms improving independent of the areas of disease excised.

Ovarian endometriosis is particularly problematic because treatment for pain may involve extensive surgery that compromises future fertility, for the women who desire it. Excisional treatment has been identified to be superior to fenestration or ablation for pain symptoms including dysmenorrhea, dyspareunia, and nonmenstrual pain, with a lower chance of recurrence at 5 years; however, this must always be balanced against ovarian cortical damage [51−53]. For ovarian disease, the adage "the first go is the best go" seems to hold weight with recurrent treatment of ovarian disease having a substantial impact on ovarian reserve, and this must be discussed with the patient [54]. In addition, it is a requirement that all disease must be removed from the side wall to prevent the persistence of disease being mistaken for the recurrence of disease. This requires a high degree of surgical skill because ureteric, vascular, and neurologic dissections are often required.

Perhaps the most recent change in the field of endometriosis surgery comes from an RCT that compares segmental and disc resections for disease involving the rectum [55]. This is the first RCT in this field and suggests that there is no clinical difference when performing major bowel surgery for endometriosis by expert hands. In addition, it changes the previous notion that disc resection is both less invasive with lower risk of complication than segmental resection. That view is likely to have arisen because a systematic review [56] of 49 nonrandomized studies on bowel surgery for endometriosis have reported that more women achieve complete pain relief when segmental bowel resection is undertaken compared with disc resection. One-third of studies in the review did not report pain outcomes, and of those that did, only 16 of 33 (48%) studies had a mean follow-up of more than 24 months.

In this case, evidence from an RCT should initiate a change in our thinking and practice because there may be little difference in either clinical outcome or complication rate for any type of excisional surgery involving the bowel. The consent must be thorough no matter which approach is used, and a high degree of surgical skill and collaboration with other disciplines for low-volume gynecologic surgeons seem prudent. What would be optimal is an RCT of bowel surgery vs sham surgery for pain symptoms to take that next step to compare not just 2 techniques but the benefit of surgery vs the conservative approach. Such a study seems unlikely.

The reports of PSN for obstinate dysmenorrhea were published as early as in 1937 [57] and involved the division of T10 to L1 sympathetic nerves on the anterior surface of the sacrum. With only a single RCT reporting only an improvement in dysmenorrhea and the risk of long-term complications such as constipation and urinary urgency, the use of this procedure must be questioned. The data for the use of LUNA demonstrate that there is no substantive improvement in pain when this technique is used over standard surgery alone. If we truly want to adhere to evidence-based practice, then this is a technique that needs to be abandoned as it has no demonstrable clinical effect and is based on very tenuous biologic plausibility from the outset.

Conclusion

Endometriosis-associated pelvic pain remains one of the most complex gynecologic presentations. RCTs are seen as the cornerstone of good evidence-based practice, and for endometriosis care, there are a handful of trials relating to pain that provide a foundation for what we currently do. The best available evidence to date, extracted from blinded studies, suggests that the removal of lesions is superior to not removing lesions. These studies do not denote a difference between superficial disease and more severe, deep disease; however, only 17 women have been included in a blinded, randomized, excisional surgical trial. It is apparent that further studies are required, but mounting such studies in the age of information sharing over the internet is likely to prevent equipoise in both patients and researchers alike.

The presence of deep endometriosis may require special surgical skills and necessitate working in a multidisciplinary team. When deep disease is identified, the aim should be to remove all disease to improve pain outcomes, as shown in prospective and retrospective studies. The approach to surgery does not impact the outcome of pain, although other factors may be affected. There is no role of LUNA in our surgical armamentarium, and the place of PSN needs to be limited and should not be considered outside a research setting because of the marginal improvement in studies to date.

Surgery will likely always have a role in the management of pelvic pain due to endometriosis. Because of the limitations of surgical RCTs and the variance in endometriosis disease expression, definitive answers about the best surgical techniques for a given woman's symptoms may be unrealistic.

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