Surgical Outcomes in Patients With Endometriosis: A Systematic Review



S.S. Singh

Sukhbir S. Singh, MD;¹ Kerstin Gude, PhD;² Elizabeth Perdeaux, PhD;³ William T. Gattrell, PhD;^{3,4} Christian M. Becker, MD⁵

¹Department of Obstetrics and Gynecology, The Ottawa Hospital & University of Ottawa, Ottawa, ON

²Global Pharmacovigilance, Bayer AG, Berlin, Germany

³Research Evaluation Unit, Oxford PharmaGenesis, Oxford, United Kingdom

⁴Department of Mechanical Engineering and Mathematical Sciences, Oxford Brookes University, Oxford, United Kingdom

⁵Endometriosis Care and Research (CaRe) Centre, Nuffield Department of Women's and Reproductive Health, University of Oxford, Oxford, United Kingdom

Abstract

- **Objective:** Among women treated surgically for endometriosisassociated pain, comprehensive data are lacking on the proportions of patients who experience little or no symptom relief, develop recurrent symptoms, or require further surgical treatment for endometriosis. The aim of this study was to assess the efficacy of surgical procedures used to treat endometriosis-associated pain.
- **Methods:** Medline and Embase were searched on October 13, 2016. Articles referring to women undergoing surgery for the treatment of endometriosis-associated pain were screened by two independent investigators. For each included treatment arm, data were extracted for the proportion of patients reporting partial or no improvement after surgery for endometriosis-associated pain, pain recurrence, or requirement for further surgery.
- **Results:** A total of 38 studies were included. Most studies did not report relevant outcomes to evaluate pain (71.1%) and recurrent surgery (68.4%). Of the women who underwent lesion excision, 11.8% reported no improvement in pain, and 22.6% underwent further surgery. Postoperative pain, recurrent pain, and adverse events were reported by 34.3%, 28.7%, and 14.8%, respectively, of patients who underwent excision or ablation of endometriosis combined with pelvic denervation and in 25.0%, 15.8%, and 8.1% of women who underwent lesion excision alone. Of the patients who were treated surgically for deep endometriosis affecting the bowel and/or bladder, 7.0% experienced recurrent symptoms, and 4.1% underwent further surgery.
- **Conclusion:** This review supports the findings of previous studies and highlights the need for standardized reporting and more detailed follow-up after surgery for endometriosis-associated pain.

Key Words: Endometriosis, pain, surgery, systematic review

Corresponding author: Dr. Sukhbir S. Singh, Department of Obstetrics and Gynecology, Ottawa Hospital Research Institute, Ottawa, ON. susingh@toh.ca

Competing Interests: See Acknowledgements.

The authors have indicated that they meet the journal's requirements for authorship.

Received on March 18, 2019

Accepted on August 1, 2019

Résumé

- **Objectif**: Pour les femmes ayant reçu un traitement chirurgical des douleurs liées à l'endométriose, on observe un manque de données sur la proportion de patientes qui éprouvent un soulagement partiel ou inexistant de leurs symptômes, qui connaissent une récidive des symptômes ou qui nécessitent des traitements chirurgicaux supplémentaires. Cette étude visait à évaluer l'efficacité des interventions chirurgicales utilisées pour traiter les douleurs liées à l'endométriose.
- Méthodologie : Des recherches ont été menées dans Medline et Embase le 13 octobre 2016. Deux chercheurs indépendants ont évalué des articles faisant référence aux femmes qui subissent une intervention chirurgicale pour traiter les douleurs liées à l'endométriose. Pour chaque volet de traitement retenu, les données ont été extraites pour la portion de patientes qui rapportaient une amélioration partielle ou inexistante après une intervention chirurgicale pour traiter les douleurs liées à l'endométriose, présentaient une récidive des douleurs ou nécessitaient une intervention chirurgicale supplémentaire.
- Résultats : Un total de 38 études ont été retenues. La plupart des études ne rapportaient pas de données pertinentes pour évaluer les douleurs (71,1%) ni les interventions chirurgicales supplémentaires (68,4%). Parmi les femmes qui ont subi une excision des lésions, 11,8% ont rapporté ne ressentir aucune amélioration des douleurs et 22,6% ont dû subir une intervention chirurgicale supplémentaire. On a rapporté des douleurs postopératoires, des douleurs récidivantes et des événements défavorables respectivement chez 34,3%, 28,7% et 14,8% des patientes qui ont subi une excision ou une ablation de l'endométriose combinée à une dénervation pelvienne et chez 25.0%. 15.8% et 8.1% des patientes qui ont subi une excision des lésions seulement. Des patientes qui ont subi un traitement chirurgical d'une atteinte endométriosique profonde du côlon et/ou de la vessie, 7,0% ont connu une récidive des symptômes et 4,1% ont subi une intervention chirurgicale supplémentaire.
- **Conclusion :** Cette revue corrobore les conclusions d'études précédentes et fait ressortir le besoin d'uniformisation des déclarations et d'un suivi postopératoire détaillé après un traitement chirurgical des douleurs liées à l'endométriose.

© 2019 The Society of Obstetricians and Gynaecologists of Canada/La Société des obstétriciens et gynécologues du Canada. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license. (http://creativecommons.org/licenses/by-nc-nd/4.0/)

J Obstet Gynaecol Can 2019;000(000):1-8 https://doi.org/10.1016/j.jogc.2019.08.004

INTRODUCTION

E ndometriotic lesions most commonly form on the peritoneum, ovaries, bowel, and bladder and can cause adhesions between pelvic organs.¹ For many women, endometriosis-associated pain (chronic pelvic pain, dysmenorrhoea, dyspareunia, dysuria, dyschezia) can have a significant impact on health-related quality of life.^{2,3}

The recommended surgical approach to manage endometriosis-associated pain depends on the type of lesion. Surgical excision or ablation is recommended for superficial lesions and full excision for deep endometriosis (previously termed "deep infiltrating endometriosis") and endometriomas.⁴ In some cases, radical surgery may be required to alleviate endometriosis-associated pain, such as pre-sacral neurectomy or hysterectomy with removal of the ovaries.⁵ Conservative surgery, in which the uterus and at least one ovary are preserved, is the preferred approach in women who want to preserve fertility.⁶ Medical treatments such as analgesics and hormonal agents may also be given as a preoperative or postoperative adjunct to surgery or as an alternative treatment strategy.⁴

In clinical studies, 20% to 38% of patients reported no improvement in endometriosis-associated pain following surgery.^{7,8} The probability of pain recurrence was 24% at 3 years.⁹ However, comprehensive data are lacking for the proportion of patients who experience little or no pain relief, develop recurrent pain, or require further surgical treatment for endometriosis. Comparisons of these parameters are hampered by a lack of standardized approaches to postsurgical therapy and by sparse use of validated, standardized assessment tools in endometriosis trials.

The aim of this systematic review was to assess the response, recurrence, and reoperation rates for the full range of surgical procedures used to treat endometriosis-associated pain to determine their effectiveness and evaluate the need for new therapies.

METHODS

Search Strategy

Medline and Embase were searched using Ovid on October 13, 2016, to identify all studies reporting response to surgery for the treatment of endometriosis-associated pain (Figure); the search strings are provided in online Table 1. After removal of duplicates, all identified references were screened and categorized by two independent investigators. Prospective or retrospective studies evaluating the surgical treatment of endometriosis and reporting any of the following outcomes of interest were included: treatment response according to type of surgery or location of lesions, recurrence rate of endometriosis-associated pain or lesions, and number of women requiring further surgical treatment.

Exclusion criteria were as follows: studies with fewer than 50 patients, follow-up duration of less than 6 months, studies of patients who received hormonal treatment after surgery, and articles that did not investigate endometri-osis-associated pain as an outcome (Figure). The search

Figure. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of systematic searches and selection process.



AE: adverse event.

was limited to English-language articles with an abstract available. No limit was set for the year of publication. The protocol has been registered with PROSPERO (ID: CRD42015017831). Articles were initially screened by title only; those meeting the exclusion criteria were removed. The remaining references were screened on the basis of abstracts and/or full text.

Data Analysis

For articles that were included in the study, data were extracted to calculate the proportions of patients reporting partial or no improvement in endometriosis-associated pain after surgery. Data for endometriosis-associated pain recurrence, reoperation rates, and adverse events (AEs) following surgery were also obtained.

For data analysis, papers were categorized into seven groups, according to type of intervention: diagnostic surgery, lesion excision (including endometrioma excision), lesion ablation, endometrioma drainage without cyst excision (herein referred to as the endometrioma drainage group), pelvic denervation, hysterectomy with or without ovarian preservation, and excision of deep endometriosis. Online Table 2 lists all the surgical techniques by group. Patients in the diagnostic surgery group underwent laparoscopy for diagnostic purposes but did not receive any surgical treatment.

In this review article, the findings are presented as medians (ranges are shown only in the tables and figures) or as single values.

RESULTS

Studies Meeting the Eligibility Criteria

Of 2185 articles identified, 38 were included in this study^{8,10–46} (Figure). The main reasons for exclusion were use of medical therapy (n = 353), insufficient cohort size (n = 253), gynaecological cancer studies (n = 252), and "other" (n = 691).

Characteristics of Studies

Of the 38 studies, 65.8% were prospective, including 11 randomized controlled trials (RCTs) and one extension of an RCT, whereas 11 (28.9%) were retrospective cohort analyses, and one (2.6%) was a longitudinal study (Table 1). When categorized by intervention type, the two groups with the greatest number of surgical techniques were the lesion excision (14 techniques) and deep endometriosis (11 techniques) groups (online Table 2). Median duration of follow-up varied widely across the seven groups, ranging from 9 months for lesion ablation to 92 months for hysterectomy (Table 1).

Table 1. Characteristic	cs of studies inclu	uded in the review				
Treatment type	Number of studies (number of treatment arms)	Study type	Median number of patients ^a	Total number of patients	Median follow- up, months	Publication year
Diagnostic surgery	2 (1)	RCT (n = 1) ⁸ ; extension of RCT (n = 1) ³³	I	31	18	1994-1997
Directed lesion excision	25 (31)	RCT (n = 9) ^{12,13,26,28,31,38,41,44,45} , prospective cohort study (n = 8) ^{15,18,20,23,35,40,42,43} , retrospective cohort study (n = 7) ^{19,21,27,29,30,34,36} , longitudinal unmatched study (n = 1) ³⁹	66	2652	24	1988-2016
Directed lesion ablation	2 (2)	Prospective cohort study $(n = 1)^{25}$; RCT $(n = 1)^{13}$	64	128	თ	2005-2010
Endometrioma drainage without cyst excision	3 (3)	RCT (n = 2) ^{26.31} ; retrospective cohort study (n = 1) ²⁹	48	150	24	1998-2004
Pelvic denervation	7 (6)	RCT (n = 4) ^{8.28.38.41} ; extension of RCT (n = 1) ³³ ; prospective cohort study (n = $2)^{32.37}$	57.5	369	24	1992-2003
Hysterectomy	1 (2)	Retrospective cohort study (n = 1) ¹⁹	48.5	97	92	2008
Deep endometriosis affecting the bowel and/or bladder	8 (11)	Retrospective cohort study (n = 4) ^{10,17,22,46} ; prospective cohort study (n = 3) ^{14,16,24} ; RCT (n = 1) ¹¹	63	1553	30	2005-2016
The number of patients who co	ompleted the study.					
RCT: randomized clinical trial.						

Table 2. Main outcome measures by surgery type

Surgery type	No reduction in pain, %	Persistence of pain after surgery, %	Recurrent pain, %	Recurrent surgery, %	Change in VAS score from baseline, cm	AEs/women, n/N
Diagnostic surgery	77.4	ND	ND	77.4	+0.3	0/31
Lesion excision	11.8 (3.6–22.2)	25.0 (4.4-41.7)	15.8 (0.0-42.0)	22.6 (5.8–56.9)	-3.6	124/1527
Lesion ablation	11.4	ND	ND	ND	-2.4	0/79
Endometrioma drainage only	ND	ND	54.8 (52.9-75.0)	51.5 (22.9-80.0)	ND	0/32
Pelvic denervation	6.7 (5.8–15.0)	34.3 (8.6–48.1)	28.7 (10.0-36.0)	12.5	-2.2	27/182
Hysterectomy with ovarian preservation	ND	ND	ND	19.1	ND	ND
Hysterectomy without ovarian preservation	ND	ND	ND	8.0	ND	ND
Deep endometriosis affecting the bowel and/or bladder	0.0 (0.0-4.4)	2.3 (2.2–4.4)	7.0	4.1 (1.3–27.6)	-6.2	63/779
AE: adverse event; ND: no data; VAS	: visual analogue sca	le.				

Values are median proportion of women (range) except for change in pain VAS score and AEs.

The pelvic denervation group included seven studies; uterine nerve ablation in an RCT (data were pooled with the extension study),^{8,33} uterosacral ligament resection in another RCT,^{8,28} and pre-sacral neurectomy in four studies^{32,37,38,41} (online Table 2). Pelvic denervation was performed in combination with lesion excision or ablation in four studies. Directed lesion excision was the most common treatment class, reported in 25 studies and across 31 treatment arms. The effectiveness of hysterectomy was investigated in only one study.¹⁹ Eight studies exclusively included women with deep endometriosis; all studies in this group assessed the efficacy of lesion excision.

The effect of surgical treatment on endometriosis-associated pain was investigated in 23 studies, $^{10,11,13-20,22}$, $^{24-26,28,30,34,39,41-44}$ whereas the remaining 15 studies investigated AEs and/or other symptom recurrence. 12,21,23,27,29 , $^{31-33,35-38,40,45,46}$ Quantitative assessments of endometriosis-associated pain before and/or after treatment were performed in 20 of the 23 studies that investigated this outcome: 18 (90.0%) used a 10-cm visual analogue scale (VAS), $^{8,10,11,13-18,20-23,28,39,41-44}$ and two (10.0%) used the Visick score or a 10-point subjective scale. 17,34 Only 14 studies reported both baseline and postoperative VAS scores for endometriosis-associated pain.

Proportion of Patients With No Reduction in Endometriosis-Associated Pain

Only 11 studies (28.9%) reported the number of women with no reduction in endometriosis-associated pain immediately after surgery. Most women (77.4%) who underwent diagnostic surgery (one treatment arm; n = 31) reported no reduction in pain (Table 2, online Table 3, online Figure 1A).³³ Few women experienced no reduction in pain immediately following lesion excision (median 11.8%; five treatment arms; n = 371),^{15,18,20,30,40} lesion ablation (11.4%; one treatment arm; n = 79),²⁵ pelvic denervation (median 6.7%; three treatment arms; n = 184),^{32,33,37} or surgery for deep endometriosis (median 0%; three treatment arms; n = 276).^{11,17}

Proportion of Patients With Persistent Endometriosis-Associated Pain After Surgery

Nine studies (23.7%) reported the number of women who experienced some, but not complete, pain relief following surgery. The proportions of women who experienced incomplete relief of pain were as follows: 34.3% in the pelvic denervation group (two treatment arms; n = 87),^{37,38} 25.0% in the lesion excision group (six treatment arms; n = 407),^{15,18,20,30,38,40} and 2.3% in the deep endometriosis group (two treatment arms; n = 213)^{11,17} (Table 2, online Table 4, online Figure 1B).

Proportion of Patients With Recurrent Endometriosis-Associated Pain

Twelve studies (31.6%) reported data on recurrence of endometriosis-associated pain following surgery. More than one half (54.8%) of the women who underwent endometrioma drainage (two treatment arms; n = 80)^{26,31} experienced recurrence of pain (Table 2, online Table 5, online Figure 1C). In other treatment groups, the proportions of women who experienced pain recurrence were as follows: 28.7% in the pelvic denervation group (three treatment arms; n = 157),^{28,33,38} 15.8% in the lesion excision group (12 treatment arms; n = 921),^{12,26–28,31,34,35,38,40,45}

and 7.0% in the deep endometriosis group (one treatment arm; n = 54).²²

Proportion of Patients Requiring Further Surgery

Twelve studies (31.6%) reported the proportion of women who required further surgery. Most women who underwent diagnostic surgery (77.4%; one treatment arm; n = 31)³³ or endometrioma drainage (51.5%; two treatment arms; n = 118)^{26,29} required further surgery (Table 2, online Table 6, online Figure 2). Further surgical procedures were required by 22.6% of women after lesion excision (five treatment arms; n = 747),^{19,26,29,39,40} 12.5% after pelvic denervation to reduce endometriosis-associated pain (one treatment arm; n = 32),³³ 19.1% after hysterectomy with ovarian preservation (one treatment arm; n = 47) and 8.0% without ovarian preservation (one treatment arm; n = 50),¹⁹ and 4.1% in the deep endometriosis group (eight treatment arms; n = 514).^{11,14,16,17,22,46}

Only one study reported outcomes following reoperation: complete resolution of disease was achieved in two patients with ureteral endometriosis in the deep endometriosis group.²²

Reduction in Visual Analogue Scale Score From Baseline

More than one third of studies (36.8%) reported both baseline and postoperative VAS scores for endometriosis-associated pain. The median reduction in VAS 10-cm scores from baseline to the end of follow-up (median 12 months, unless specified otherwise) was as follows: -6.2 cm in the deep endometriosis group (22 months follow-up; 11 treatment arms; n = 263),^{11,14,16} - 3.6 cm in the lesion excision group (25 treatment arms; n = 713),^{13,15,18,20,28,41-44} - 2.4 cm in the lesion ablation group (six treatment arms; n = 49),¹³ and -2.2 cm in the pelvic denervation group (seven treatment arms; n = 185)^{8,28,41} (Table 2, online Table 7, online Figure 3). Women who underwent diagnostic surgery experienced a 0.3-cm increase in VAS score from 7.5 cm (6 months follow-up; one treatment arm; n = 31).⁸

Adverse Events Following Surgery for Endometriosis

Twenty-three studies (60.5%) reported on AEs following surgery. In the pelvic denervation group (four treatment arms), 27 AEs were reported in 182 patients (AE rate, 14.8%) (Table 2, online Table 8).^{8,37,38,41} The most common AEs in this group were severe constipation (n = 16) and urinary retention (n = 4). Rare AEs included retroperitoneal pre-sacral hematoma (n = 1), hemorrhage from the middle sacral vein (n = 1), and painless labour (n = 1). In the lesion excision group (17 treatment arms), 124 AEs were reported

in 1527 patients (8.1%).^{12,15,18,21,30,31,34–36,39–41} The most common AEs were blood loss (n = 43), postoperative fever (n = 9), and urinary retention (n = 9). Sixty-three AEs in 779 patients (8.1%) were reported in the deep endometriosis group (10 treatment arms). The most common AEs were urinary retention (n = 13), leakage of the bowel anastomosis (n = 7), and severe stenosis of the anastomosis (n = 6).^{11,14,16,17,22,24,46} No complications were reported following laparoscopy for lesion ablation (one treatment arm; n = 79),²⁵ endometrioma drainage (one treatment arm; n = 32),³¹ or diagnostic surgery (one treatment arm; n = 31).⁸

DISCUSSION

Main Findings and Interpretation

Surgery represents one of the pillars of modern management of endometriosis-associated pain.⁴ However, the surgical outcomes were not reported in most of the 38 clinical studies identified as relevant in this systematic review. Less than one third of studies reported the number of women without a reduction in pain, with incomplete pain relief, with recurrence of pain, or with need for further surgery. Approximately 40% of studies did not report AE data. Three studies reported that there were no complications following laparoscopy for lesion ablation, endometrioma drainage, or diagnostic surgery.^{8,25,31} Although laparoscopy is not without risk, it is considered to be the gold standard surgical treatment because of its lower morbidity and shorter hospital stays than laparotomy.⁴⁷

The available data suggest that one fourth of women who underwent lesion excision reported having some remaining endometriosis-associated pain following surgery and that, in general, more than 10% reported no improvement in pain. More than 15% of women experienced recurrent endometriosis-associated pain, and one fifth underwent further surgery. Data were insufficient to draw direct comparisons regarding the efficacy of lesion excision and ablation, although one 5-year study showed that patients were less likely to need medical therapy for endometriosis after lesion excision than after lesion ablation.⁴⁸ Moreover, our study does suggest that patients who receive lesion ablation therapy experience fewer AEs than patients whose lesions are excised. Similarly, only 6% of clinicians who responded to a survey thought that lesion excision is safer than lesion ablation.49

In two systematic reviews of RCTs, uterine nerve ablation did not provide greater pain relief than excision of endometriotic lesions.^{50,51} In contrast, pre-sacral neurectomy with conservative surgery provides superior pain relief to conservative surgery alone at 12 months,^{38,41} although the

technique should only be performed by highly skilled surgeons owing to the high risk of AEs.^{4,5} In this study, uterine nerve ablation and pre-sacral neurectomy were combined into a single treatment group because of the limited number of available studies and low patient numbers. Overall, few women (6.7%) who underwent pelvic denervation reported no reduction in endometriosis-associated pain following treatment; however, one third experienced an incomplete response, and one third reported symptom recurrence. Furthermore, AEs were common in this group, with more than one half being severe constipation.

Previous studies have reported that surgical treatment of bowel deep endometriosis leads to substantial pain relief, with low recurrence rates (3% to 7%).^{52,53} Consistent with this, our study showed that women with deep endometriosis have a good prognosis following surgery. Few women with deep endometriosis experienced incomplete relief or no relief of endometriosis-associated pain, recurrence of pain symptoms, or AEs after surgery. Indeed, surgical treatment of deep endometriosis-associated pain reduction as measured by VAS. However, the deep endometriosis studies were performed by experts in high-volume centres, meaning that these results may not represent the real-world expertise of gynaecologists globally and that their generalizability is limited.

In this review, patients who underwent hysterectomy with ovarian preservation were more than twice as likely to require further surgical treatment than patients who underwent hysterectomy without ovarian preservation (18.1% vs. 9.0%). It has been reported previously that, compared with bilateral oophorectomy, ovarian preservation is associated with a six-fold increase in recurrence of endometriosis-associated pain and an eight-fold greater risk of reoperation.⁵⁴ Given the occurrence of serious AEs,⁵⁵ however, hysterectomy with bilateral oophorectomy is often reserved for women whose symptoms did not respond to earlier therapy.⁵

The findings of this study highlight the need for greater, more detailed, and more consistent reporting of the efficacy of surgical interventions for endometriosis-associated pain. We found limited data for the proportion of patients who experienced incomplete endometriosis-associated pain reduction, pain recurrence, or reoperation in the hysterectomy and lesion ablation groups. Most outcomes were reported in one third of studies or less, and evaluation of the outcomes data was difficult because of the diversity of parameters investigated. This finding is consistent with a previous systematic review in which 29 trials, 32 outcomes, and 24 measures were used to assess endometriosis-associated pain.⁵⁶ Such incomplete and inconsistent reporting makes it difficult to draw conclusions regarding the effectiveness and safety of these treatments. Therefore, initiatives such as Core Outcomes in Women's and Newborn Health (CROWN), which was developed to harmonize outcome reporting in women's health research, and the World Endometriosis Research Foundation (WERF) Endometriosis Phenome and Biobanking Harmonisation Project (EPHect), which was developed to standardize data and sample collection in endometriosis, are essential for progress in the future.^{57,58}

The medical management of endometriosis-associated pain is well recognized as a beneficial intervention either as a prelude to considering surgical management or postoperatively to prevent the recurrence of pain.⁵ The endometriosis-associated pain VAS scores reported at baseline in this review (5.5–7.5 cm) were similar to those found in our previous systematic review exploring the treatment of endometriosis with various medical therapies (5.5–6.1 cm).⁵⁹ Moreover, the combined findings of our systematic reviews indicate that there is a lack of clear, consistent data concerning the long-term pain relief that patients may expect following medical or surgical treatment for endometriosis. Thus, providing women with clear, evidence-based recommendations regarding the most appropriate treatment options remains difficult.⁵⁹

Strengths, Limitations, and Sources of Bias in the Findings

This systematic review provides useful information on surgical practices and outcomes in women with endometriosis. However, it is important to note that this review focused on surgical interventions only. In clinical practice, physicians most commonly combine medical and surgical interventions to treat endometriosis-associated pain. It is possible, therefore, that differences in medical treatment patterns may have introduced bias in relation to the effectiveness of surgery in this review and in the source studies. Furthermore, because many of the published studies were conducted at centres of expertise specializing in endometriosis management, the findings may not be generalizable throughout the gynaecology community.

Other factors that may have influenced or biased the findings include the designs of the source studies (e.g., the presence or absence of blinding or randomization), patient characteristics, and lack of consistency among the source studies when reporting lesion locations and outcomes. Several different surgical techniques were used to treat endometriosis-associated pain, particularly in the lesion excision and deep endometriosis groups. Efficacy and AEs were not analyzed by route of surgery because the surgical technique was not consistently reported in all studies. Furthermore, the diversity of the patient cohorts, even within individual studies, is likely to have influenced our findings. For example, young age at disease onset, chronic endometriosis-associated pain, time following treatment, and more severe disease are risk factors for multiple surgical interventions for endometriosis.⁶⁰ Patient characteristics such as age will also have influenced the choice of surgical treatment. Although the heterogeneity of the patient population reflects clinical practice, it complicates direct comparisons across studies or treatment groups, and it may account for the wide ranges in some data. In addition, evaluation of the outcomes data was complicated because of the diversity of methods used to assess endometriosis-associated pain. Further factors impeding comparison among studies, and which could have introduced bias in the findings, include differences in follow-up times and changing standards of care over the study period.

CONCLUSION

To improve the care provided to women experiencing endometriosis-associated pain, a systematic and defined approach to the study of interventions is required. Research on the long-term effectiveness of surgery appears to be in its infancy, and, as a result, the ability to counsel women on outcomes of management is limited at this time.

Acknowledgements

The authors thank Andreas Leidenroth, PhD for assisting in the screening of article abstracts. This study was funded by Bayer AG. Dr. Singh has participated in a speakers' bureau; has received research grants and consulting fees from Abb-Vie, Allergan, and Bayer AG (independent of the submitted work); and has received consulting fees from Cooper Surgical. Dr. Gude is a full-time employee of Bayer AG. Dr. Perdeaux is an employee of Oxford PharmaGenesis, which received funding for both the study and medical writing services from Bayer AG. Dr. Gattrell is a former employee of Oxford PharmaGenesis, which received funding for both the study and medical writing services from Bayer AG; and is now an employee of Ipsen Pharma. Dr. Becker has received research grants from Bayer AG, independent of the submitted work, Volition RX, MDNA Life Sciences and Roche Diagnostics. He has received consultancy fees from Myovant and AbbVie and is a member of the independent data monitoring board for ObsEva. He is the current chair of the Endometriosis Guideline Development group for ESHRE. Drs. Singh and Becker have not received any payment for their participation in this work and remain independent of Bayer AG.

REFERENCES

- Fauconnier A, Chapron C. Endometriosis and pelvic pain: epidemiological evidence of the relationship and implications. Hum Reprod Update 2005;11:595–606.
- Nnoaham KE, Hummelshoj L, Webster P, et al. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. Fertil Steril 2011;96:366–73. e8.
- Sinaii N, Plumb K, Cotton L, et al. Differences in characteristics among 1,000 women with endometriosis based on extent of disease. Fertil Steril 2008;89:538–45.
- Johnson NP, Hummelshoj L, World Endometriosis Society Montpellier Consortium. Consensus on current management of endometriosis. Hum Reprod 2013;28:1552–68.
- Dunselman GA, Vermeulen N, Becker C, et al. ESHRE guideline: management of women with endometriosis. Hum Reprod 2014;29:400–12.
- 6. Kim SH, Chae HD, Kim CH, et al. Update on the treatment of endometriosis. Clin Exp Reprod Med 2013;40:55–9.
- 7. Abbott J, Hawe J, Hunter D, et al. Laparoscopic excision of endometriosis: a randomized, placebo-controlled trial. Fertil Steril 2004;82:878–84.
- Sutton CJ, Ewen SP, Whitelaw N, et al. Prospective, randomized, double-blind, controlled trial of laser laparoscopy in the treatment of pelvic pain associated with minimal, mild, and moderate endometriosis. Fertil Steril 1994;62:696–700.
- Vercellini P, Fedele L, Aimi G, et al. Reproductive performance, pain recurrence and disease relapse after conservative surgical treatment for endometriosis: the predictive value of the current classification system. Hum Reprod 2006;21:2679–85.
- Ruffo G, Scopelliti F, Manzoni A, et al. Long-term outcome after laparoscopic bowel resections for deep infiltrating endometriosis: a singlecenter experience after 900 cases. Biomed Res Int 2014;2014:463058.
- Che X, Huang X, Zhang J, et al. Is nerve-sparing surgery suitable for deeply infiltrating endometriosis? Eur J Obstet Gynecol Reprod Biol 2014;175:87– 91 https://doi.org/10.1016/j.ejogrb.2014.01.027.
- 12. Mossa B, Ebano V, Tucci S, et al. Laparoscopic surgery for the management of ovarian endometriomas. Med Sci Monit 2010;16:MT45–50.
- Healey M, Ang WC, Cheng C. Surgical treatment of endometriosis: a prospective randomized double-blinded trial comparing excision and ablation. Fertil Steril 2010;94:2536–40.
- Chapron C, Bourret A, Chopin N, et al. Surgery for bladder endometriosis: long-term results and concomitant management of associated posterior deep lesions. Hum Reprod 2010;25:884–9.
- Seracchioli R, Mabrouk M, Montanari G, et al. Conservative laparoscopic management of urinary tract endometriosis (UTE): surgical outcome and long-term follow-up. Fertil Steril 2010;94:856–61.
- Camanni M, Bonino L, Delpiano EM, et al. Laparoscopic conservative management of ureteral endometriosis: a survey of eighty patients submitted to ureterolysis. Reprod Biol Endocrinol 2009;7:109.
- Pereira RM, Zanatta A, Preti CD, et al. Should the gynecologist perform laparoscopic bowel resection to treat endometriosis? Results over 7 years in 168 patients. J Minim Invasive Gynecol 2009;16:472–9.
- Darai E, Ackerman G, Bazot M, et al. Laparoscopic segmental colorectal resection for endometriosis: limits and complications. Surg Endosc 2007;21:1572–7.
- Shakiba K, Bena JF, McGill KM, et al. Surgical treatment of endometriosis: a 7-year follow-up on the requirement for further surgery. Obstet Gynecol 2008;111:1285–92.
- Ferrero S, Abbamonte LH, Giordano M, et al. Deep dyspareunia and sex life after laparoscopic excision of endometriosis. Hum Reprod 2007;22:1142–8.

- **21.** Brouwer R, Woods RJ. Rectal endometriosis: results of radical excision and review of published work. Aust N Z J Surg 2007;77:562–71.
- Frenna V, Santos L, Ohana E, et al. Laparoscopic management of ureteral endometriosis: our experience. J Minim Invasive Gynecol 2007;14:169–71.
- 23. Milingos S, Protopapas A, Kallipolitis G, et al. Endometriosis in patients with chronic pelvic pain: is staging predictive of the efficacy of laparoscopic surgery in pain relief? Gynecol Obstet Invest 2006;62:48–54.
- Keckstein J, Wiesinger H. Deep endometriosis, including intestinal involvement—the interdisciplinary approach. Minim Invasive Ther Allied Technol 2005;14:160–6.
- Nardo LG, Moustafa M, Gareth Beynon DW. Laparoscopic treatment of pelvic pain associated with minimal and mild endometriosis with use of the Helica Thermal Coagulator. Fertil Steril 2005;83:735–8.
- **26.** Alborzi S, Momtahan M, Parsanezhad ME, et al. A prospective, randomized study comparing laparoscopic ovarian cystectomy versus fenestration and coagulation in patients with endometriomas. Fertil Steril 2004;82:1633–7.
- 27. Fedele L, Bianchi S, Zanconato G, et al. Long-term follow-up after conservative surgery for rectovaginal endometriosis. Am J Obstet Gynecol 2004;190:1020-4.
- **28.** Vercellini P, Aimi G, Busacca M, et al. Laparoscopic uterosacral ligament resection for dysmenorrhea associated with endometriosis: results of a randomized, controlled trial. Fertil Steril 2003;80:310–9.
- 29. Saleh A, Tulandi T. Reoperation after laparoscopic treatment of ovarian endometriomas by excision and by fenestration. Fertil Steril 1999;72:322–4.
- Chapron C, Dubuisson JB, Fritel X, et al. Operative management of deep endometriosis infiltrating the uterosacral ligaments. J Am Assoc Gynecol Laparosc 1999;6:31–7.
- Beretta P, Franchi M, Ghezzi F, et al. Randomized clinical trial of two laparoscopic treatments of endometriomas: cystectomy versus drainage and coagulation. Fertil Steril 1998;70:1176–80.
- 32. Nezhat CH, Seidman DS, Nezhat FR, et al. Long-term outcome of laparoscopic presacral neurectomy for the treatment of central pelvic pain attributed to endometriosis. Obstet Gynecol 1998;91:701–4.
- 33. Sutton CJ, Pooley AS, Ewen SP, et al. Follow-up report on a randomized controlled trial of laser laparoscopy in the treatment of pelvic pain associated with minimal to moderate endometriosis. Fertil Steril 1997;68:1070–4.
- Sutton CJ, Ewen SP, Jacobs SA, et al. Laser laparoscopic surgery in the treatment of ovarian endometriomas. J Am Assoc Gynecol Laparosc 1997;4:319–23.
- 35. Donnez J, Nisolle M, Gillerot S, et al. Rectovaginal septum adenomyotic nodules: a series of 500 cases. Br J Obstet Gynaecol 1997;104:1014–8.
- 36. Catalano GF, Marana R, Caruana P, et al. Laparoscopy versus microsurgery by laparotomy for excision of ovarian cysts in patients with moderate or severe endometriosis. J Am Assoc Gynecol Laparosc 1996;3:267–70.
- Nezhat C, Nezhat F. A simplified method of laparoscopic presacral neurectomy for the treatment of central pelvic pain due to endometriosis. Br J Obstet Gynaecol 1992;99:659–63.
- Candiani GB, Fedele L, Vercellini P, et al. Presacral neurectomy for the treatment of pelvic pain associated with endometriosis: a controlled study. Am J Obstet Gynecol 1992;167:100–3.
- Redwine DB. Conservative laparoscopic excision of endometriosis by sharp dissection: life table analysis of reoperation and persistent or recurrent disease. Fertil Steril 1991;56:628–34.
- 40. Davis GD, Brooks RA. Excision of pelvic endometriosis with the carbon dioxide laser laparoscope. Obstet Gynecol 1988;72:816–9.
- Zullo F, Palomba S, Zupi E, et al. Effectiveness of presacral neurectomy in women with severe dysmenorrhea caused by endometriosis who were treated with laparoscopic conservative surgery: a 1-year prospective randomized double-blind controlled trial. Am J Obstet Gynecol 2003;189:5–10.

- Lukic A, Di Properzio M, De Carlo S, et al. Quality of sex life in endometriosis patients with deep dyspareunia before and after laparoscopic treatment. Arch Gynecol Obstet 2016;293:583–90.
- 43. Fritzer N, Tammaa A, Haas D, et al. When sex is not on fire: a prospective multicentre study evaluating the short-term effects of radical resection of endometriosis on quality of sex life and dyspareunia. Eur J Obstet Gynecol Reprod Biol 2016;197:36–40.
- 44. Gallicchio L, Helzlsouer KJ, Audlin KM, et al. Change in pain and quality of life among women enrolled in a trial examining the use of narrow band imaging during laparoscopic surgery for suspected endometriosis. J Minim Invasive Gynecol 2015;22:1208–14.
- **45.** Mettler L, Ruprai R, Alkatout I. Impact of medical and surgical treatment of endometriosis on the cure of endometriosis and pain. Biomed Res Int 2014;2014:264653.
- 46. Afors K, Centini G, Fernandes R, et al. Segmental and discoid resection are preferential to bowel shaving for medium-term symptomatic relief in patients with bowel endometriosis. J Minim Invasive Gynecol 2016;23:1123–9.
- Chapron C, Querleu D, Bruhat MA, et al. Surgical complications of diagnostic and operative gynaecological laparoscopy: a series of 29,966 cases. Hum Reprod 1998;13:867–72.
- Healey M, Cheng C, Kaur H. To excise or ablate endometriosis? A prospective randomized double-blinded trial after 5-year follow-up. J Minim Invasive Gynecol 2014;21:999–1004.
- **49.** Moses SH, Clark TJ. Current practice for the laparoscopic diagnosis and treatment of endometriosis: a national questionnaire survey of consultant gynaecologists in UK. BJOG 2004;111:1269–72.
- Proctor ML, Latthe PM, Farquhar CM, et al. Surgical interruption of pelvic nerve pathways for primary and secondary dysmenorrhoea. Cochrane Database Syst Rev 2005(4):CD001896.
- Latthe PM, Proctor ML, Farquhar CM, et al. Surgical interruption of pelvic nerve pathways in dysmenorrhea: a systematic review of effectiveness. Acta Obstet Gynecol Scand 2007;86:4–15.
- Wolthuis AM, Meuleman C, Tomassetti C, et al. Bowel endometriosis: colorectal surgeon's perspective in a multidisciplinary surgical team. World J Gastroenterol 2014;20:15616–23.
- 53. De Cicco C, Corona R, Schonman R, et al. Bowel resection for deep endometriosis: a systematic review. BJOG 2011;118:285–91.
- Rizk B, Fischer AS, Lotfy HA, et al. Recurrence of endometriosis after hysterectomy. Facts Views Vis Obgyn 2014;6:219–27.
- McPherson K, Metcalfe MA, Herbert A, et al. Severe complications of hysterectomy: the VALUE study. BJOG 2004;111:688–94.
- Hirsch M, Duffy JM, Kusznir JO, et al. Variation in outcome reporting in endometriosis trials: a systematic review. Am J Obstet Gynecol 2016;214:452–64.
- 57. Khan K. The CROWN Initiative: journal editors invite researchers to develop core outcomes in women's health. BJOG 2014;121:1181–2.
- Becker CM, Laufer MR, Stratton P, et al. World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonisation Project: I. Surgical phenotype data collection in endometriosis research. Fertil Steril 2014;102:1213–22.
- Becker CM, Gattrell WT, Gude K, et al. Reevaluating response and failure of medical treatment of endometriosis: a systematic review. Fertil Steril 2017;108:125–36.
- Cheong Y, Tay P, Luk F, et al. Laparoscopic surgery for endometriosis: how often do we need to re-operate? J Obstet Gynaecol 2008;28:82–5.

Table S1. Summary of search of MEDLINE $^{\otimes}$ and Embase $^{\otimes},$ performed using Ovid $^{\otimes}$ on October 13, 2016

#	Search history	Results
1	[Terms for endometriosis]	0
2	ENDOMETRIOSIS/	49 624
3	(adenomyo\$ or endometrio\$).tw.	64 559
4	chocolate cyst\$.tw.	328
5	or/2-4	73 165
6	[Terms for surgery]	0
7	SURGERY/	766 685
8	surgery.tw.	2 135 307
9	surgical.tw.	1 791 424
10	EXCISION/	55 727
11	excis\$.tw.	335 491
12	ablation.tw.	171 603
13	adhesioly\$.tw.	3384
14	cystectomy.tw.	28 893
15	CYSTECTOMY/	28 604
16	nodulectomy.tw.	182
17	NODULECTOMY/	10
18	resect\$.tw.	674 757
19	presacral neurectomy.tw.	210
20	(uterosacral nerve ablation or LUNA).tw.	1955
21	(plasmajet or plasma jet).tw.	502
22	HYSTERECTOMY/	70 401
23	hysterectomy.tw.	71 471
24	LAPAROSCOPY/	142 496
25	laparoscop\$.tw.	253 729
26	or/7-25	4 174 725
27	[Terms for symptoms]	0
28	PAIN/	491 678
29	pain\$.tw.	1 316 769
30	PELVIC PAIN/	7959
31	pelvic pain.tw.	18 272
32	CHRONIC PELVIC PAIN/	11 741
33	chronic pelvic pain.tw.	7661
34	((adenomyo\$ or endometriosis\$) adj2 pain\$).tw.	1255
35	dyspareunia.tw.	8503
36	dysmenorrh?ea.tw.	10 755
37	dyschezia.tw.	636
38	dysuria.tw.	8989
39	LESION/	265
40	lesion\$.tw.	1 667 361
41	cyst?.tw.	225 529
42	nodule?.tw.	160 173

(continued)

Tab	le S1. (Continued)	
#	Search history	Results
43	recurr#n\$.tw.	1 075 904
44	or/28-43	4 119 259
45	[Terms for outcomes]	0
46	(re-operation or reoperation).tw.	59 154
47	improv\$.tw.	4 269 583
48	reduc\$.tw.	6 002 399
49	effect\$.tw.	12 372 399
50	(relief or reliev\$).tw.	277 973
51	outcome.tw.	1 810 512
52	complication\$.tw.	1 723 876
53	rate?.tw.	5 192 973
54	or/46-53	21 395 247
55	5 and 26 and 44 and 54	9610
56	[Filters]	0
57	55 and (wom#n or patient?).tw.	8787
58	57 and (randomi\$ or clinic\$ or trial\$ or observa- tion\$ or database or prospective or retrospec- tive or cohort or study or series).tw.	6685
59	58 not (mice or murine or mouse or baboon\$ or monkey\$ or animal\$ or rabbit\$ or polymorphi\$ or apopto\$).tw.	6483
60	conference abstract.af.	2 355 040
61	59 not 60	4925
62	limit 61 to abstracts	4912
63	limit 62 to English language	4319
64	limit 63 to "review"	549
65	63 not 64	3770
66	remove duplicates from 65	2185

Table S2. Surgical techniques used in each treatment group

Treatment group	Surgical techniques ^a (number of studies)
Diagnostic surgery	Diagnostic laparoscopy (n = 1)
Lesion excision	Laparoscopic lesion excision (n = 15); laser laparoscopy (n = 4); conservative surgery (n = 3); segmental colorectal resection (n = 3); laparoscopic partial cystectomy (n = 2); laparotomy (n = 2); cystectomy (n = 1); dissection of endometriosis from rectal wall (n = 1); full-thickness excision of anterior rectal wall (n = 1); laparoscopic stripping technique (n = 1); laparoscopic ureterolysis (n = 1); partial bladder resection (n = 1); segmental ureteral resection and ureteroureterostomy (n = 1); ureterectomy and ureterocystoneostomy (n = 1)
Lesion ablation	Laparoscopic ablation (n = 1); cauterization/ablation with Helica thermal coagulator (n = 1)
Endometrioma drainage only	Fenestration and coagulation (n = 3)
Pelvic denervation	Presacral neurectomy (n = 4); uterine nerve ablation (n = 2); uterosacral ligament resection (n = 1)
Hysterectomy	Hysterectomy with ovarian preservation ($n = 1$); hysterectomy without ovarian preservation ($n = 1$)
Deep endometriosis	Bowel resection (n = 6); ureterolysis (n = 3); full/partial cystectomy (n = 3); lesion excision (n = 3); salpingo-oophorectomy (n = 2); hysterectomy (n = 2); ureteroneocystostomy (n = 1); unilateral salpingectomy (n = 1); uterine nerve ablation (n = 1); ureteral reimplantation (n = 1); rectal shaving (n = 1)
^a The inclusion of surgical techniques was b	ased on the treatment arms in the studies. Not all of the studies differentiated between laparoscopy and laparotomy.



Figure S1. Response to therapy and symptom recurrence after surgical treatment for endometriosis.

Data are presented as median (range) or single values; median follow-up time (Figure S1C only); total numbers of women who completed the study.

DE: deep endometriosis; ND: no data.

Table S3. Proporti	on of patients with no	reduction in p	pain following surg	ical treat	ment of endome	etriosis				
Treatment class	Study	Total symptoms, %	Dysmenorrhoea, %	Pelvic pain, %	Dyspareunia, %	Dyschezia, %	Other, %	Median non-response rate (range), %	Number of patients ^a	Total number of patients
Diagnostic surgery	Sutton <i>et al</i> ., 1997a	77.4	ND	ND	ND	ND	ND	77.4	31	31
Lesion excision	Seracchioli et al., 2010	3.6	ND	ND	ND	ND	ND	11.8 (3.6–22.2)	56	371
	Darai <i>et al</i> ., 2007	ND	8.2	ND	12.3	19.4	22.2		71	
	Ferrero et al., 2007	ND	ND	ND	4.4	ND	ND		68	
	Chapron et al., 1999	ND	17.6	ND	11.8	ND	ND		110	
	Davis & Brooks, 1988	6.1	ND	ND	ND	ND	ND		66	
Lesion ablation	Nardo <i>et al</i> ., 2005	11.4	ND	ND	ND	ND	ND	11.4	79	79
Pelvic denervation	Sutton <i>et al</i> ., 1997a	6.3	ND	ND	ND	ND	ND	6.7 (5.8–15.0)	32	184
	Nezhat <i>et al</i> ., 1998	ND	15.0	6.7	ND	ND	ND		100	
	Nezhat & Nezhat, 1992	ND	7.7	5.8	ND	ND	ND		52	
Deep endometriosis	Che <i>et al</i> ., 2014	0.0	ND	ND	ND	ND	ND	0.0 (0.0-4.4)	63	276
	Che <i>et al.</i> , 2014	4.4	ND	ND	ND	ND	ND		45	
	Pereira <i>et al.</i> , 2009	0.0	0.0	0.0	0.0	0.0	0.0		168	

^a The number of patients who completed the study. There were no data for patients who underwent endometrioma drainage only or hysterectomy with/without ovarian preservation.

ND: no data.

	ion of patients with pe	i sistence or p	and following surgi		nem of endome	110313				
Treatment class	Study	Total symptoms, %	Dysmenorrhoea, %	Pelvic pain, %	Dyspareunia, %	Dyschezia, %	Other, %	Median (range), %	Number of patients ^a	Total number of patients
Lesion excision	Seracchioli et al., 2010	ND	ND	ND	ND	ND	32.1	25.0 (4.4-41.7)	56	407
	Darai <i>et al.</i> , 2007	ND	36.6	ND	29.6	23.9	35.2		71	
	Ferrero et al., 2007	ND	ND	ND	4.4	ND	ND		68	
	Chapron <i>et al.</i> , 1999	ND	31.8	ND	22.4	ND	ND		110	
	Candiani <i>et al</i> ., 1992	ND	41.7	13.9	19.4	ND	ND		36	
	Davis & Brooks, 1988	ND	ND	25.0	5.6	ND	ND		66	
Pelvic denervation	Nezhat & Nezhat, 1992	ND	48.1	48.1	ND	ND	ND	34.3 (8.6–48.1)	52	87
	Candiani <i>et al</i> ., 1992	ND	34.3	8.6	11.4	ND	ND		35	
Deep endometriosis	Che et al., 2014	ND	4.4	2.2	2.2	ND	ND	2.3 (2.2-4.4)	45	213
	Pereira <i>et al.</i> , 2009	2.4	ND	ND	ND	ND	ND		168	

Table S4. Proportion of patients with persistence of pain following surgical treatment of endometriosis

^a The number of patients who completed the study.

There were no data for patients who underwent diagnostic surgery, lesion ablation surgery, endometrioma drainage only or hysterectomy with/without ovarian preservation.

ND: no data.

Figure S2. Proportion of patients requiring further surgical treatment for endometriosis.

DE	Hysterectomy (without ovarian preservation)	Hysterectomy (with ovarian preservation)	Pelvic denervation	Endometrioma drainage only	Lesion ablation	Lesion excision	Diagnostic surgery
4.1% (1.3–27.6%); 30 months; n = 514; 8 treatment arms 20 40 60 80 100 Proportion of patients (%)	8.0%; 92 months; n = 50; 1 treatment arm	19.1%; 92 months; n = 47; 1 treatment arm	12.5%; 18 months; n = 32; 1 treatment arm	2 treatment arms	ND 51.5% (22.9–80.0%);	22.6% (5.8–56.9%); 24 months; n = 747; 5 treatment arms	77.4%; 18-month follow-up; n = 31; 1 treatment arm I

Data are presented as median (range) or single values; median follow-up time; total numbers of women who completed the study. DE: deep endometriosis; ND: no data.

Treatment class	Study ^a	Total symptoms,	Dysmenorrhoea, %	Pelvic pain, %	Dyspareunia, %	Median (range), %	Number of patients ^b	Total number of patients	Follow-up, months	Median follow-up (range), months
Lesion excision	Mossa <i>et al</i> ., 2010	ND	6.4	2.1	2.1	15.8 (0.0-42.0)	47	921	12	22 (6.0-37.5)
	Mossa <i>et al</i> ., 2010	ND	4.7	0.0	2.3		43		12	
	Alborzi <i>et al</i> ., 2004	15.8	ND	ND	ND		52		24	
	Fedele <i>et al</i> ., 2004	28.0	25.3	19.3	25.3		83		37.5	
	Vercellini et al., 2003	ND	32.0	ND	ND		90		36	
	Beretta <i>et al</i> ., 1998	ND	15.8	10.0	20		32		19.5	
	Donnez et al., 1997	ND	ND	3.7	1.2		242		24	
	Sutton <i>et al</i> ., 1997b	30.0	ND	ND	ND		64		24	
	Sutton <i>et al</i> ., 1997b	12.5	ND	ND	ND		29		36	
	Candiani <i>et al</i> ., 1992	ND	42.0	42.0	ND		36		12	
	Davis & Brooks, 1988	7.6	ND	ND	ND		66		12	
	Mettler et al., 2014	ND	20.0	24.0	15.0		137		6	
Endometrioma drainage	Alborzi <i>et al</i> ., 2004	56.7	ND	ND	ND	54.8 (52.9-75.0)	48	80	24	22 (20-24)
	Beretta <i>et al</i> ., 1998	ND	52.9	52.9	75.0		32		20	
Pelvic denervation	Vercellini et al., 2003	ND	36.0	ND	ND	28.7 (10.0-36.0)	90	157	36	18 (12–36)
	Candiani <i>et al</i> ., 1992	ND	34.3	23.0	ND		35		12	
	Sutton <i>et al</i> ., 1997a	10.0	ND	ND	ND		32		18	
Deep endometriosis	Frenna <i>et al.</i> , 2007	7.0	ND	ND	ND	7.0	54	54	9	9

Table S5. Proportion of patients with recurrence of pain following surgical treatment of endometriosis

^a Different treatment arms within the same study are listed individually.

^b The number of patients who completed the study.

There were no data for patients who underwent diagnostic surgery, lesion ablation surgery or hysterectomy with/without ovarian preservation.

ND: no data.



Figure S3. VAS score (cm) for total pain symptoms at baseline and after follow-up.

VAS scores shown as median (range). Follow-up data shown as median follow-up time (range); total numbers of women who completed the study; number of treatment arm(s).

DE: deep endometriosis; VAS: visual analogue scale.

Table S6. Proportion of pat	ients requiring further su	rgical treatment for	r endometriosis				
Treatment class	Study	Proportion, %	Median (range), %	Number of patients ^a	Total number of patients	Follow-up, months	Median follow-up (range), months
Diagnostic surgery	Sutton <i>et al</i> ., 1997a	77.4	77.4	31	31	18	18
Lesion excision	Shakiba <i>et al</i> ., 2008	56.9	22.6 (5.8–56.9)	109	747	92	24 (12–92)
	Alborzi <i>et al.</i> , 2004	5.8		52		24	
	Saleh & Tulandi, 1999	23.0		161		36	
	Redwine, 1991	22.6		359		24	
	Davis & Brooks, 1988	21.2		66		12	
Endometrioma drainage	Alborzi <i>et al.</i> , 2004	22.9	51.5 (22.9-80.0)	48	118	24	30 (24-36)
	Saleh & Tulandi, 1999	80.0		70		36	
Pelvic denervation	Sutton <i>et al.</i> , 1997a	12.5	12.5	32	32	18	18
Hysterectomy (with ovarian preservation)	Shakiba <i>et al.</i> , 2008	19.1	19.1	47	47	92	92
Hysterectomy (without ovarian preservation)	Shakiba <i>et al</i> ., 2008	8.0	8.0	50	50	92	92
Deep endometriosis	Che <i>et al.</i> , 2014	4.4	4.1 (1.3–27.6)	45	514	21	30 (9–60)
	Chapron et al., 2010	1.3		75		60	
	Camanni <i>et al.</i> , 2009	2.5		80		22	
	Pereira et al., 2009	3.6		168		37	
	Frenna <i>et al.</i> , 2007	3.7		54		9	
	Afors et al., 2016	27.6		47		30	
	Afors et al., 2016	13.3		15		30	
	Afors <i>et al.</i> , 2016	6.6		30		30	

^a The number of patients who completed the study. There were no data for patients who underwent lesion ablation surgery.

ND: no data.

Treatment class	Study ^a	Number of patients ^b	Follow-up, months	Pain symptom	Baseline VAS, cm	Follow-up VAS, cm	Median baseline VAS, cm	Median follow-up VAS, cm	Change in median VAS from baseline to follow-up, cm	Total number of patients	Median follow-up (range), months
Diagnostic surgery	Sutton et al., 1994	31	6	Total symptoms	7.5	7.8	7.5	7.8	+0.3	31	6
Lesion excision	Healey <i>et al.</i> , 2010	54	12	Dysmenorrhoea	6.4	3.8	5.5 (1.2-8.1)	1.9 (0.1–5.4)	-3.6	713	12 (6–55)
	Healey et al., 2010			Dyspareunia	5.6	1.9					
	Healey <i>et al.</i> , 2010			Dysuria	1.2	0.6					
	Healey et al., 2010			Dyschezia	3.6	1.8					
	Healey et al., 2010			Total symptoms	5.5	2.4					
	Healey et al., 2010			Pelvic pain	6.0	3.2					
	Seracchioli et al., 2010	56	55	Dysuria	4.0	0.1					
	Seracchioli et al., 2010			Other	3.1	0.6					
	Darai <i>et al</i> ., 2007	71	24	Dysmenorrhoea	7.5	1.8					
	Darai <i>et al.</i> , 2007			Dyspareunia	5.6	1.8					
	Darai <i>et al</i> ., 2007			Dyschezia	3.4	1.7					
	Darai <i>et al.</i> , 2007			Other	4.8	2.2					
	Darai <i>et al</i> ., 2007			Other	4.5	1.9					
	Darai <i>et al</i> ., 2007			Other	4.5	1.4					
	Ferrero et al., 2007	68	12	Dyspareunia	7.6	2.6					
	Vercellini et al., 2003	90	36	Dysmenorrhoea	7.6	4.0					
	Vercellini et al., 2003			Dyspareunia	5.4	1.8					
	Vercellini et al., 2003			Pelvic pain	3.5	2.0					
	Zullo et al., 2003	63	12	Dysmenorrhoea	8.1	5.4					
	Zullo et al., 2003			Dyspareunia	6.3	4.9					
	Zullo et al., 2003			Pelvic pain	6.2	5.0					
	Lukic <i>et al.</i> , 2016	67	6	Dyspareunia	7.8	3.5					
	Gallichio et al., 2015	100	6	Pelvic pain	5.0	1.1					
	Gallichio et al., 2015	38	6	Pelvic pain	4.0	1.0					
	Fritzer et al., 2016	96	8	Dyspareunia	6.2	2.5					
Lesion ablation	Healey et al., 2010	49	12	Total symptoms	6.2	3.2	5.7 (1.7-7.1)	3.3 (0.9-4.8)	-2.4	49	12
	Healey et al., 2010			Pelvic pain	6.8	4.0					
	Healey et al., 2010			Dysmenorrhoea	7.1	4.8					
	Healey <i>et al.</i> , 2010			Dyspareunia	5.2	3.3					
	Healey et al., 2010			Dysuria	1.7	0.9					
	Healev <i>et al.</i> , 2010			Dvschezia	2.9	2.3					

(continued on next page)

Treatment class	Study ^a	Number of patients ^b	Follow-up, months	Pain symptom	Baseline VAS, cm	Follow-up VAS, cm	Median baseline VAS, cm	Median follow-up VAS, cm	Change in median VAS from baseline to follow-up, cm	Total number of patients	Median follow-up (range), months
Pelvic denervation	Sutton <i>et al</i> ., 1994	32	6	Total symptoms	8.5	4.8	6.5 (5.5-8.5)	4.3 (2.2-4.8)	-2.2	185	12 (6-36)
	Vercellini et al., 2003	90	36	Pelvic pain	5.5	2.5					
	Vercellini et al., 2003			Dysmenorrhoea	7.8	3.8					
	Vercellini et al., 2003			Dyspareunia	6.0	2.2					
	Zullo et al., 2003	63	12	Pelvic pain	6.3	4.3					
	Zullo et al., 2003			Dysmenorrhoea	8.3	4.6					
	Zullo et al., 2003			Dyspareunia	6.5	4.4					
Deep endometriosis	Che <i>et al.</i> , 2014	63	22	Total symptoms	7.1	1.8	6.8 (2.8-8.0)	0.6 (0.0-2.2)	-6.2	263	22 (21-60)
	Che et al., 2014	45	21	Total symptoms	6.8	2.1					
	Chapron et al., 2010	75	60	Pelvic pain	2.8	0.8					
	Chapron et al., 2010			Dysmenorrhoea	7.8	2.2					
	Chapron <i>et al</i> ., 2010			Dyspareunia	6.0	0.9					
	Chapron et al., 2010			Other	3.1	0.6					
	Chapron <i>et al</i> ., 2010			Other	5.9	0.4					
	Camanni <i>et al.</i> , 2009	80	22	Dysmenorrhoea	8.0	0.0					
	Camanni <i>et al</i> ., 2009			Dyspareunia	6.0	0.0					
	Camanni <i>et al.</i> , 2009			Dysuria	7.0	0.0					
	Camanni <i>et al.</i> , 2009			Dyschezia	7.0	0.0					

^b The number of patients who completed the study.

VAS: visual analogue scale.

Table S8. Number of adverse events in different treatment groups

Treatment type	Study ^a	Number of patients	Number of AEs	Follow-up time, months	Total number of patients ^b	Total number of AEs	Median follow-up time (range), months
Diagnostic surgery	Sutton <i>et al.</i> , 1994	31	0	6	31	0	6
Lesion excision	Mossa <i>et al.</i> , 2010	47	3	12	1527	124	24 (12–68)
	Mossa <i>et al</i> ., 2010	43	32	12			
	Seracchioli et al., 2010	56	12	55			
	Darai <i>et al</i> ., 2007	71	9	24			
	Brouwer & Woods, 2007	18	3	68			
	Brouwer & Woods, 2007	58	2	68			
	Brouwer & Woods, 2007	137	11	68			
	Chapron et al., 1999	110	9	21			
	Beretta et al., 1998	32	0	20			
	Donnez <i>et al</i> ., 1997	242	10	24			
	Sutton <i>et al</i> ., 1997b	64	0	36			
	Sutton et al., 1997b	29	0	36			
	Catalano et al., 1996	83	1	32			
	Catalano et al., 1996	49	9	35			
	Redwine, 1991	359	2	24			
	Davis & Brooks, 1988	66	21	12			
	Zullo <i>et al.</i> , 2003	63	0	12			
Lesion ablation	Nardo et al., 2005	79	0	6	79	0	6
Endometrioma drainage	Beretta <i>et al.</i> , 1998	32	0	19.5	32	0	19.5
Pelvic denervation	Nezhat & Nezhat, 1992	52	7	12	182	27	12 (6-12)
	Candiani <i>et al</i> ., 1992	35	17	12			
	Zullo et al., 2003	63	3	12			
	Sutton <i>et al.</i> , 1994	32	0	6			
Deep endometriosis affecting the bowel and/or bladder	Che <i>et al</i> ., 2014	63	9	22	779	63	30 (9–60)
	Che <i>et al</i> ., 2014	45	0	21			
	Chapron <i>et al.</i> , 2010	75	2	60			
	Camanni <i>et al</i> ., 2009	80	3	22			
	Pereira <i>et al.</i> , 2009	168	13	37			
	Frenna <i>et al.</i> , 2007	54	4	9			
	Keckstein & Wiesinger, 2005	202	15	ND			
	Afors et al., 2016	47	10	30			
	Afors et al., 2016	15	3	30			
	Afors et al., 2016	30	4	30			

^a Different treatment arms within the same study are listed individually.

^b The number of patients who completed the study.

AE: adverse event; ND: no data.