BMJ Open

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|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2017-018924 |
| Article Type: | Research |
| Date Submitted by the Author: | 01-Sep-2017 |
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| Primary Subject Heading: | Obstetrics and gynaecology |
| Secondary Subject Heading: | Obstetrics and gynaecology |
| Keywords: | Laparoscopy, bowel endometriosis, deep infiltrating endometriosis, rectal endometriosis, rectovaginal endometriosis |
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**Title**

# Laparoscopic excision of deep rectovaginal endometriosis in BSGE Endometriosis Centres: A multicentre prospective cohort study

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**Abstract**

Objective**:** To estimate the effectiveness and safety of laparoscopic surgical excision of rectovaginal endometriosis.

Design**:** A multicentre, prospective cohort study

Setting**:** 51 hospitals accredited as specialist Endometriosis Centres.

Participants**:** 5,162 women of reproductive age with rectovaginal endometriosis of which 4,721 women had planned laparoscopic excision.

Interventions**:** Laparoscopic surgical excision of rectovaginal endometriosis requiring dissection of the para-rectal space.

Main outcome measures: Standardised symptom questionnaires enquiring about chronic pelvic pain, bladder and bowel symptoms, analgesia use and quality of life measured using the EuroQol instrument completed prior to surgery and at 6, 12 and 24 months post-operatively. Serious peri- and post-operative complications including major haemorrhage, infection and visceral injury were recorded.

Results: At 6 months post surgery there were significant reductions in premenstrual, menstrual and non-cyclical pelvic pain, deep dyspareunia, dyschezia, low back pain and bladder pain. In addition, there were significant reductions in voiding difficulty, bowel frequency, urgency, incomplete emptying, constipation and passing blood. These reductions were maintained at two years, with the exception of voiding difficulty. Global quality of life significantly improved from a median pre-treatment score of 55/100 to 80/100 at six months, as well as a significant improvement in quality of life in all measured domains. These improvements were sustained at two years. All analgesia use was reduced and in particular opiate use fell from 28.1% prior to surgery to 16.1% at six months. The overall incidence of complications was 6.8% (321/4721). Gastrointestinal complications (enterotomy,

anastomotic leak or fistula) occurred in 52 (1.1%) operations and of the urinary tract (ureteric / bladder injury or leak) in 49 (1.0%) procedures.

Conclusion: Laparoscopic surgical excision of rectovaginal endometriosis appears to be effective in treating pelvic pain and bowel symptoms and improving health-related quality of life and has a low rate of major complications when performed in specialist centres.

Keywords: Laparoscopy; bowel endometriosis; deep infiltrating endometriosis; rectal endometriosis; rectovaginal endometriosis

**Article summary – Strengths and limitations**

- Our study is by far the largest , multcentre observational cohort published for the laparoscopic surgical treatment of rectovaginal endometriosis with a sample of nearly 5000 cases.
- Data were prospectively collected, minimising missing data and recall bias, were obtained from multiple centres enhancing transferability, and outcomes measurements were patient reported reducing interpreter bias.
- Efficacy outcomes were assessed in both the short term (at six months) and longer term (at two years) following surgery. In addition, the scale of these data and the method of collection have enabled a robust assessment of the risk of complications from this type of surgery. The reported incidence of complications cannot however, be used as indicative risk for patients who have care given in non-specialist endometriosis centres.
- The main limitation of our study relates to missing data from incomplete data entry, incomplete follow-up or uncompleted follow up at closure of the study. We performed sensitivity analyses to explore the robustness of our results to incomplete. The results were stable, remaining significant in some cases even when symptomatic outcomes for those women with missing data were assumed to be the worst possible outcome.
- The study would have benefited from a non-surgically treated control group, however, denying surgery to a group of women with severe, refractory symptoms makes the conduct of such a study problematic and of questionable feasibility. Thus historical control data were used from the same patients prior to surgical intervention.

## Introduction

Endometriosis is a common and serious problem for women in their reproductive years and can cause chronic pelvic pain, subfertility, bowel and urinary dysfunction.[1] The associated morbidity places a substantial economic burden on society as a result of direct healthcare costs and indirect productivity losses. In the USA, direct healthcare costs have been estimated to be $2,801 annually per patient with an additional cost of $1,023 annually per patient due to loss of productivity. Overall the costs associated with endometriosis in the USA are estimated at 22 billion dollars per annum.[2]

Deep endometriosis in the posterior pelvis frequently affects the space between the anterior wall of the rectosigmoid and the posterior vaginal wall and is usually referred to as rectovaginal endometriosis. There is limited evidence supporting the sustained effectiveness and acceptability of medical therapies in improving the symptoms of rectovaginal endometriosis.[3–5] Consequently surgical treatment has been proposed to completely excise the deep rectovaginal disease.[6–8]

Advances in instrumentation and surgical experience have led to laparoscopic treatment superseding alternative surgical routes such as laparotomy and transvaginal excision. Previous studies have reported improvements in generic quality of life data following surgical excision of endometriosis involving the bowel, but these evaluations have been undertaken using small cohorts of women usually from single centres, affecting the precision and generalisability of the derived results.[9–11] Whilst these findings of improved symptomatic outcomes are promising, it is well recognised that surgery for deep endometriosis with bowel involvement is complex and can be associated with serious and potentially life threatening complications.[10] For these reasons, the ESHRE Guidelines on the 'Management of women with endometriosis' recommend that clinicians refer women with suspected or diagnosed

deep endometriosis to a centre of expertise that offers all available treatments in a multidisciplinary context.[1]

In 2006 the British Society for Gynaecological Endoscopy (BSGE) developed specialist endometriosis centres (Endocentres), where patients would be treated by surgeons who work in multidisciplinary teams, audit their outcomes and perform sufficient workload to maintain their surgical skills.[12]

In view of the paucity of world literature data pertaining to the effectiveness and safety of this highly complex surgery for a common gynaecological condition, we undertook a prospective, multi-centre cohort study to estimate (i) effectiveness of surgery on patient reported symptoms associated with endometriosis as well as its impact upon women's health related quality of life and (ii) safety by examining rates of surgical complications using data collected from the BSGE Endocentres dataset.

## Methods

### *Study design*

A multicentre prospective cohort study of pre-menopausal women undergoing surgery for pelvic pain associated with rectovaginal disease resistant to medical treatment or conservative surgical therapy rectovaginal disease was performed. Standardised diagnostic, operative, histological and patient outcome data were prospectively collected from 51 BSGE Endometriosis centres between 1st January 2009 and 30th June 2016.

### *Study population*

Women treated in a BSGE Endocentre who underwent laparoscopic excision of deep rectovaginal endometriosis, which required dissection of the pararectal space and gave written consent for data collection were included in the study. Dissection of the pararectal

space was chosen as the inclusion criterion for cases to be studied because access to this anatomical space is necessary to free adherent bowel prior to excision of deep rectovaginal disease. Furthermore, this operative step is necessary irrespective of the type of surgery performed on the bowel. So by choosing this step of the surgical procedure the BSGE could be assured that all cases of deep rectovaginal endometriosis would be included reducing the risk of selection bias. Clear explanation of dissection of the deep pararectal space is provided on the BSGE endometriosis database for surgeons. Whilst there have been a number of historical scoring systems for endometriosis, some were not developed prior to the inception of the BSGE project and none have been universally accepted.[13–16] In order to retain accreditation as a BSGE Endocentre, all consenting patients who undergo surgery for deep rectovaginal endometriosis that includes dissection of the pararectal space in an Endocentre must have their data entered on to the BSGE national endometriosis database.

*Clinical data*

Standardised patient symptom data and quality of life (QoL) assessments were collected prior to surgery as a baseline control. The assessments were repeated at six months, one year and two years after surgery. To ensure consistent timing of follow-up, the database only accepts post-operative data entry within an interval from four weeks before the exact date required and up to eight weeks after the exact date.

All patients recorded their clinical symptoms on a BSGE standard questionnaire using a 0-10 point Likert scale for premenstrual pain, menstrual pain, non cyclical pelvic pain, deep dyspareunia, cyclical dyschezia, non cyclical dyschezia, lower back pain, bladder pain and voiding difficulty. In addition, patients recorded details of bowel function with graded answers for; frequency of bowel movement, urgency of bowel movement, incomplete empyting sensation, constipation and blood in the stool. Patient reported quality of life data were collected using EuroQuol 5D questionnaire and EuroQuol Visual Analogue Score.[17,18]

Dichotomous data (‘yes or ‘no’) were collected for use of analgesia (parcetamol, non

steroidal anti-inflammatory drug (NSAID) or opiates) and medical therapy (oral contraceptive pill, Mirena Intrauterine system™ (Bayer, Germany), GNRH analogues alone, GNRH analogues plus add back hormone replacement, systemic progestogens or aromatase inhibitors).

*Surgical data*

Details of previous endometriosis surgery were recorded including adnexal surgery and hysterectomy. Surgical details were collected using a standard dataset describing the name and level of the surgeon, whether a colorectal and/or a urological surgeon also undertook the surgery and whether the surgery was laparoscopic or laparotomic. The distribution of any endometriosis deposits was described by 'yes' or 'no', for right and left pelvic side-wall, right and left endometrioma, right and left uterosacral ligament and obliteration of the pouch of Douglas. Bowel involvement of endometriosis was also recorded dichotomously for 'rectal involvement', 'rectovaginal nodule', or involvement of 'appendix', 'small bowel' and 'rectosigmoid'. Co-existent bladder endometriosis was recorded by yes or no for superficial bladder, deep bladder and deep utero-vesical endometriosis.

The surgeon recorded the surgical procedure for each of the above areas of distribution of endometriosis from a list of; 'ablated', 'excised', 'ablated and excised', 'not treated' or 'not present'. Surgery on any endometrioma present was recorded by selecting from a list of; 'ablated', 'excised', 'oophorectomy', 'drained only', 'not treated' or 'not applicable'. Pararectal space dissected was recorded as yes or no. Surgery on a rectovaginal nodule was recorded as 'ablated', 'excised', 'not treated' or 'not applicable'. Opening of the vagina as part of the surgery was recorded as 'yes', 'no' or 'not applicable'. The type of bowel surgery was recorded by selecting from a list of; 'not applicable', 'not treated', 'shaved', 'disc resection' or 'segmental resection', along with whether a stoma was formed, or not. Surgery on any bladder endometriosis was recorded as; 'ablated', 'excised without bladder opening', 'excised with bladder opening', 'not present' or 'not treated'. Ureteric endometriosis surgery

was described by ureteric nodule excised (yes, no or not present), right ureterolysis (yes, no or not applicable), left ureterolysis (yes, no or not applicable), JJ stent (yes or no). Finally, data were collected regarding performance of a concomitant hysterectomy (yes, no or not applicable) with space for free text.

Recording of complications was divided into two sections with 'yes' or 'no' answers for a standardised list of perioperative and post operative complications. Complication data included surgical injury to urological, gastrointestinal or vascular structures, unplanned procedures including conversion to laparotomy, infective morbidity, pulmonary embolism and death. Histology of removed specimens was examined for malignant transformation.

*Statistical Methods*

Data were analysed according to the study eligibility critera, namely: a valid operation date was entered, the intended operation was via a laparoscopy, the para-rectal space was dissected and there was excision of endometriosis. If duplicate data were present, the most complete dataset was used. Centres which entered fewer than 20 cases in the total study period were excluded.

Non-numerical scores (eg: bowel symptoms) and the EuroQuol 5D-3L were coded numerically with an assumed underlying interval scale. For the patient reported data, pair-wise comparisons were made using the baseline pre-operative data as a control. We also compared the symptom scores at six months with those at two years to assess the post-operative trend. Data were thus only included if both the pre-operative and the relevant post-operative data were entered. The Mann Whitney U test (Wilcoxon rank sum) was used for comparison for data with more than two outcomes and the sign test for dichotomous data. A statistic was considered significant if the probability of it occurring by chance was $<0.05$ on a two-tailed test.

As post-operative follow-up was incomplete, the impact of this was assessed in two ways. The first method was by restricting the analysis to centres with more complete follow-up;

defined as centres performing at least 50 operations in the study period,with more than 90% of pre-operative questionnaires and more than 70% of post-operative questionnaires entered onto the BSGE database for at least one post-operative clinical follow-up period. The second method was to include all women for whom a pre-operative, baseline score was present (the controls) and use the reported post-operative results if present, but to assign a score for those patients with missing post-operative follow up data. The assigned score was the same for all patients with missing data. It was initially assigned as the best outcome possible and the significance calculation repeated. The assigned score was then changed stepwise through less desirable outcomes. The last value of the assigned score at which the outcome is still significant gives a measure of the sensitivity of the result to the missing data. If, for example, the statistic is still significant with the worst possible outcome assigned to the missing post-operative dataset then the outcome is effectively independent of the missing responses.

The data analysis was performed using Matlab (MathWorks) version R2011b.

**Results**

In BSGE Endocentres between 1st Jan 2009 and 30th June 2016, 5,162 women underwent surgery for deep rectovaginal endometriosis, which included dissection of the pararectal space. Women who underwent planned laparotomy (160; 3.1%), only had ablative treatment of their endometriosis (100; 1.9%), or had no treatment of their endometriosis (181; 3.5%) were excluded from further analysis. Thus a total of 4,721 women had planned laparoscopic excision of deep rectovaginal endometriosis in a total of 51 Endocentres. Previous surgery for endometriosis had been performed in 55.1% (2,602) of these women, with 7.0% (333) having had one ovary removed, 3.0% (141) both ovaries removed and 5.0%

(234) having had a hysterectomy. The median age of women having surgery was 35.1 years (90$^{th}$ centile range 25.9 - 44.8 years).

*Surgical findings and procedures*

At surgery endometriosis was identified on the left pelvic side wall in 69.0% (3,259) patients and on the right side wall in 57.7% (2,726). It was on the left uterosacral ligament in 78.4% (3,702) patients and the right uterosacral ligament in 70.8% (3,341). The pouch of Douglas was obliterated in 67.1% (3,167) women and a rectovaginal nodule present in 68.6% (3,238) women. There was endometriosis present on the rectum in 54.7% (2,582) women, the caecum in 1.3% (60) women, the appendix in 2.3% (110) women, small bowel in 1.6% (75) women and rectosigmoid in 18.1% (856) women. Deep uterovesical disease was present in 422 women (8.9%).

Gonadatrophin releasing hormone agonists were given to 23.0% (1087) women prior to surgery. The operation was undertaken by a senior gynaecologist in 96.4% (4,549) cases and a colorectal surgeon was present in 27.6% (1,304) cases and a urologist in 320 (6.8%) cases. Pararectal dissection was performed in all cases and ureterolysis on the left in 65.5% (3,092) and on the right in 57.1% (2,695) cases. A ureteric nodule of endometriosis was excised in 9.0% (424) and JJ ureteric stents used in 9.2% (434) cases. Bowel surgery was performed in 63.1% (2,981) cases and 1.3% (62) women had a stoma. A hysterectomy was performed in 723 (15.3%) women. Conversion to laparotomy occurred in 41 (0.9%) cases. There were no cases of malignancy in any of the endometriosis specimens.

*Follow up performance*

Whilst preoperative data were expected in 4,721 women, symptom data were available for 4,210 (89%) and QoL data for 4,041 (86%) women. At six months follow up symptom scores were available in 2,350 (50%) and QoL scores in 2241 (47%) of women. At one year post operation, data were expected for 3,977 women, of whom symptom data were present in

1499 (38%) and QoL in 1380 (35%). At two years symptom data were present in 729 (27%) and QoL data in 644 (24%) out of a possible 2,704 women.

In the seven endocentres with most complete follow up; preoperative symptom data were available for 684 (97%) of the 707 women and QoL data for 668 (94%) women. At six months symptom data were present for 537 (76%) and QoL data for 530 (75%) women. At one year post surgery, data were expected from 553 women and symptom data were present in 356 (64%) and QoL in 347 (63%) women. At two years post operation data were expected in 319 women and symptom data were present for 160 (50%) and QoL data in 145 (45%) women.

*Symptom outcomes*

At six months after laparoscopic excision of endometriosis there was a significant reduction in pain scores for premenstrual pain (from a median of 7/10 to 3/10), menstrual pain (from 9/10 to 4/10) and non cyclical pelvic pain (from 6/10 to 2/10) when compared to pre-operative scores. A significant reduction in pain scores also occurred for deep dyspareunia (from 5.5/10 to 1/10), cyclical (6/10 to 0/10) and non-cyclical dyschezia (3/10 to 0/10), low back pain (6/10 to 3/10) and a statistically significant drop in bladder pain although no change in the median score. In addition, there was a statistically significant (although not clinically significant)) reduction in voiding difficulty, bladder pain, bowel frequency, bowel urgency, incomplete bowel emptying, constipation and passing blood in the stool (see table 1).

The same significant reduction in symptoms remained present at two years post surgery for all symptoms except voiding difficulty. A comparison of the reduction in symptoms at six months was made with the reduction in symptoms at two years in order to assess the post-operative trend in symptom scores. This showed that there was a statistically significant but clinically small increase in all symptoms except voiding difficulty over the 18 months (see table 1).

Patient reported QoL for all five domains of the EuroQuol questionnaire showed a significant improvement in QoL at six months post surgery that was sustained at two years post surgery. In particular, the median global QoL on a 100 point visual analogue scale improved from 55 pre-operatively to 80 post-operatively. There was no statistically significant degradation in effect between 6 and 24 months in all measured QoL domains with the exception of the visual analogue score, which showed a statistically significant (although clinically negligible) lessening over this timeframe (see table 2, median score dropped from 80/100 to 76/100).

Analgesia use was significantly reduced at six and 24 months post surgery compared to pre-operative levels for all three analgesic types. Paracetamol use dropped from 76.0% patients to 59.8% at 6 months, NSAID use dropped from 69.8% patients to 48.9% at 6 months and opiate use dropped from 28.1% patients to 16.1% at 6 months.There was however a statistically significant (although clinically small) increase in paracetamol, NSAID and opiate use between six and 24 months post-operatively (see table 3).

*Sensitivity analyses*

Sensitivity analysis on the reduction of patient reported symptoms and the improvement in quality of life post surgery was used to estimate the effect of any incomplete data on the significance of the results and is shown in table 4. For all symptoms except voiding difficulty, constipation and blood in the stool, the median scores for missing post-operative data would have to be higher (worse) than at baseline for change in scores to become statistically non-significant. Indeed, menstrual pain scores at six months remained significantly improved on the pre-operative scores even if all the missing six month scores are assumed to be 10 (maximum pain). To further test the robustness of the data to missing values, data from the seven centres with the best follow-up were analysed separately (see table 5, supplementary tables 1-3). Improvement in premenstrual pain, menstrual pain, non-cyclical pelvic pain, deep dyspareunia, cyclical dyschezia, lower back pain and EQ-VAS were all statistically significant regardless of missing data.

*Surgical complications*

The overall incidence of complications was 6.8% (321), with perioperative complications in 4.7% (220) operations and late operative complications in 2.5% (120) women, including 19 women suffering both peri, and postoperative complications (see table 6). Bowel complications occurred in 1.1% (52 operations) and the incidence varied according to whether bowel surgery was undertaken and if so, what type of procedure; 0.6% (11) where no coexistent bowel surgery was undertaken, 1.1% (29), with bowel shaving, 9.3% (5) with disc resection and 3.9% (7) with segmental bowel resection (see table 7).

## Discussion

*Statement of principal findings*

Laparoscopic excision of severe rectovaginal endometriosis, performed in specialist centres in women with chronic pelvic pain, was associated with significant reduction in pain symptoms and improved health related quality of life. Moreover, the reduction in pain and increased quality of life observed six months following surgery was maintained at two years. All types of pain symptoms improved; pre-menstrual pain, menstrual pain, non-cyclical pain, back pain, pain with sexual intercourse, voiding and on opening the bowels. A significant reduction in the need for analgesia supported the findings of an overall reduction in pain symptoms. Bowel symptoms including frequency, urgency, incomplete emptying and constipation also improved. This type of surgery requires enhanced laparoscopic skills, primarily because of the need to overcome distorted anatomy and operate in proximity to delicate gastrointestinal, genitourinary and vascular structures. However, clinical outcomes were good, and the rates of serious peri-operative and late complications were low, when laparoscopic excision of rectovaginal endometriosis was conducted in recognised, specialist centres.

*Strengths and weaknesses of the study*

Our study has many strengths which include the size of the sample with nearly 5000 cases, the largest datset by far reported to date in the world literature. These data were collected prospectively, minimising missing data and recall bias, were obtained from multiple centres enhancing transferability, and outcomes measurements were patient reported reducing interpreter bias. Efficacy outcomes were assessed in both the short term (at six months) and longer term (at two years) following surgery. In addition, the scale of these data and the method of collection have enabled a robust assessment of the risk of complications from this type of surgery. Precise estimates of efficacy of surgery and associated complication rates to inform clinical decision making have been lacking because relevant data available in the literature have been derived from small, single centre case series [9,10,19,20] and in many such publications the severity of endometriotic disease has been heterogeneous or not defined.[9,10,19,20] We are aware of no other data set that has examined the laparoscopic management of rectovaginal endometriosis when it is applied across a country according to accepted best practice and within nationally approved guidance [6]. Although there may be some units in the UK that do not submit data to the BSGE national database, this would be the exception for any NHS unit carrying out large volumes of surgery as this has become the standard for commissioning of endometriosis services by NHS England.

The main limitation of our study relates to missing data from incomplete data entry, incomplete follow-up or uncompleted follow up at closure of the study. We performed sensitivity analyses to explore the robustness of our results to incomplete follow up. The results were stable, remaining significant in some cases even when symptomatic outcomes for those women with missing data were assumed to be the worst possible outcome. Furthermore, when we restricted analysis to the seven centres providing the most complete follow-up, the observed improvement in clinical symptoms and quality of life were reproduced. Thus, it is unlikely that the impact of missing data would substantially alter clinical inferences on the efficacy of laparoscopic surgery for severe rectovaginal endometriosis. The study would have benefited from a non-surgically treated control group,

however, denying surgery to a group of women with severe, refractory symptoms makes the conduct of such a study problematic and of questionable feasibility. Thus historical control data were used from the same patients prior to surgical intervention.

Despite the complexity of the surgery, the overall reported perioperative and post-operative serious complication rates were relatively low at 4.7% and 2.5% respectively. Conversion to laparotomy occurred in less than 1% of cases demonstrating advances in acquisition of laparoscopic surgical skills, training and equipment. Excision of endometriosis in the posterior pelvis is a difficult surgical procedure but the improved vision and precision that laparoscopy provides may improve completeness of excision and, in skilled hands, minimise the risk of complications. The ureteric injury rate of 0.5% was similar to those reported in smaller series from single centres and that associated with hysterectomy.[21] Bowel trauma, namely unintended bowel injuries, leaking from bowel surgery and recto-vaginal fistula formation occurred in 1.2% of cases. In the context of the morbidity associated with rectovaginal endometriosis, its resistance to conventional medical treatments and the nature, complexity and efficacy of surgery, this rate of complications appears to be acceptable. Moreover, the rates of adverse events are comparable to other series from expert, single centres.[19–21] The reported incidence of complications cannot however, be used as indicative risk for patients who have care given in non-specialist endometriosis centres.

*Strengths and weaknesses in relation to other studies, discussing important differences in results*

The findings from the current study which is the largest, multicentre series by far to be reported to date, are in keeping with those published from smaller, single centre observational cohorts of women undergoing laparoscopic excision of deep endometriosis. Significant reductions in the intensity of chronic pelvic pain, dysmenorrhoea, dyspareunia and dyschezia were reported from series in the UK (57 and 137 women)[11,20], Finland (22 women)[19]. The majority of studies included in a recent extensive literature review of surgical

treatment of deep endometriosis with colorectal involvement also reported improvements in pain and digestive symptoms as well as health related quality of life, although few studies reported this latter outcome.[10] The size of the 49 included studies ranged from four to 283 cases and the total number of operations evaluated were 1791 of which 679 (38%) were rectal shaving procedures, 375 (21%) disc resections and 737 (41%) segmental resections. However, comparisons between studies were not possible because of inadequate reporting (many included studies reported 'overall improvement'), as well as inconsistent assessment, of clinical outcomes (e.g. use of interviews, bespoke questionnaires, visual analogue scales). A systematic review of 34 articles describing 1889 segmental bowel resections also showed that the vast majority of women had significant improvement in chronic pelvic pain, dysmenorrhea, dyspareunia and dyschezia at one year [9].

Safety, in addition to efficacy is necessary to justify undertaking complex laparoscopic procedures for a benign pathology albeit a condition associated with substantial morbidity. Haemorrhage greater than one litre was the most common peri-operative complication occurring in 0.9% of cases. This rate is consistent with the available literature where haemorrhage requiring blood transfusion in complicated procedures (0.3%-3.1%) depending upon the type of bowel surgery.[10] Similarly our peri-operative and post-operative complication rates were comparable to the mean (range) of complications reported within a recent review of 49 case series[10]: rectovaginal fistulae 0.3% vs. 2.7% (0%-11%); enterostomy 0.5% vs. 1.2% (0.0% - 7.0%) and pelvic abscess 0.4% vs. 0.3% (0.0% - 4.0%). Complication data from a systematic review restricted to segmental bowel resection reported a 6.4% rate of severe bowel complications (leakage 1.9%; fistula 1.8%; severe obstruction 2.7%), 2.5% rate of haemorrhage and 1% severe infection rate.[9] Our ureteric injury rate of 0.5% is in keeping with the 1% reported in another series[21] as is the low observed prevalence of unintended bowel injury, major vascular injury and urinary tract fistula. [19–21]

*Meaning of the study: possible explanations and implications for clinicians and policymakers*

This study demonstrates that women having laparoscopic excisional surgery for rectovaginal endometriosis obtain significant symptomic relief, reduction in analgesia use and improvement in their quality of life. These improvements are present at six months and sustained at two years, with the exception of voiding difficulty. The lack of improvement in this symptom may be explained by the fact that the presence of bladder endometriosis was not an inclusion criterion for this study and so voiding complaints may be an independent symptom. This study cannot predict outcomes more than two years post-operatively but it is very encouraging that the worsening of symptom scores, analgesia use and quality of life scores post-operatively (from six months to two years) is extremely small compared to the large clinical improvement seen initially.

Rectovaginal endometriosis sits between the vagina and the rectum and thus the most consistent symptom differentiating it from the pain associated with less severe and other forms of endometriosis or adenomyosis, is pain on intercourse or 'dyspareunia'. In addition, in the more severe groups, pain on defaecation is a common symptom due to the proximity to, or invasion of, the bowel. Thus it is reassuring that the surgery resulted in a significant improvement in these symptoms and that the effect lasted for the two years of follow up. One of the side effects of all surgery is scarring and it is possible that a rectovaginal nodule of endometriosis excised may be replaced by scar tissue leading to a resumption of dyspareunia. These data would suggest that this was not the case. In addition the long term effects of surgery would suggest a lack of significant recurrence during the time scale of the study.

Laparoscopic surgical excision of rectovaginal endometriosis appears to be effective in treating chronic pelvic pain, bowel and urinary symptoms and improving health related quality of life and has an acceptable major complication rate when performed in specialist surgical centres. Women with severe and refractory symptoms adversely impacting on their quality of life should be offered laparoscopic surgical treatment in recognised endometriosis centres, where clinical outcomes are objectively audited. Commissioners of health services

should restrict these highly complex surgical treatments to specialist centres to ensure an adequate case-load and where expertise is demonstrated through provision of auditable clinical outcomes.

*Unanswered questions and future research*

Future studies should collect relevant baseline clinical data including comprehensive population characteristics, indications for surgery and fertility desires. Serial, standardised short and long term follow up will enhance comparability of data and a better evaluation of the longer term effects of laparoscopic interventions for deep rectovaginal disease on symptoms. Relevant and valid outcomes should be chosen with the help of patient involvement and should include valid collection of health related quality of life data. Such studies should be controlled, where possible and ideally randomised to reduce selection bias. A randomised controlled trial (RCT) comparing excisional surgery and diagnostic laparoscopy with the same number of ports is difficult ethically because women in the placebo arm would have been referred for specialist treatment and thus would be undergoing an unnecessary surgical intervention. Future studies should consider randomising between laparoscopic surgery and non-surgical therapy or alternatively compare different laparoscopic surgical interventions. The morbidity associated with rectovaginal endometriosis has a substantial economic impact due to the related reduction in activity both socially and in the work place. Thus, any future studies should include formal economic analysis to weigh the costs of surgical management against clinical, health service and societal gains.

**Conclusions**

This study presents by far the largest, multi-centre rectovaginal endometriosis surgical series in the literature both in relation to clinical outcomes and complication rates . Deep endometriosis is associated with a high disease burden and limited access to effective

medical and surgical treatment is a large unmet need. Indeed, half our study population had undergone previous surgery for endometriosis mostly in non-specialist centres. Women suffer with chronic pain and psychological symptoms which impairs their quality of life. Health services and the wider economy suffer through utilisation of substantial health care resources and restrictions placed upon women's physical functioning which can lead to absenteeism and the inability to fulfil domestic and professional duties.[22] The impact of endometriosis on quality of life is well recognised [20,23–25] and well demonstrated in the current study where the median pre-operative EQ global VAS score was only 55/100. It is also widely acknowledged that surgical management of deep endometriosis involving the rectovaginal septum and/or bowel is technically challenging and can be associated with high rates of serious complications. However, women with deep endometriosis often have severe and refractory symptoms adversely impacting on their quality of life[6–8] justifying the need for effective surgical treatment even if associated with potentially serious complications.

Our large, multicentre dataset demonstrates significant improvements in a variety of pain and functional bowel symptoms from laparoscopic excisional surgery. The substantial and sustained improvements in pain symptoms and health related quality of life and reassuringly low rates of major perioperative and post-operative complications supports this form of surgical treatment when conducted in specialist endometriosis centres. Future studies should include formal economic analyses to weigh the costs of surgical management against clinical, health service and societal gains.

**What is already known on this subject**

- Deep rectovaginal endometriosis is common, causing serious morbidity from chronic pelvic pain, subfertility, sexual dysfunction, bowel and urinary dysfunction as well as utilising health care and wider societal resources.

- Laparoscopic surgical excision is increasingly used to treat severe rectovaginal endometriosis in the absence of safe and effective medical therapy, but it requires advanced surgical skills due to its complexity and potential for serious complications.

- There is no consensus on the effectiveness and risks of laparoscopic surgical excision of rectovaginal endometriosis because evidence from large, multi-centre series with clearly defined populations are lacking.

**What this paper adds**

- Laparoscopic surgical excision of rectovaginal endometriosis appears to be effective in treating chronic pelvic pain, sexual dysfunction, bowel and urinary symptoms and improving health related quality of life and has a low major complication rate when performed in specialist surgical centres.

- Women with severe and refractory symptoms adversely impacting on their quality of life should be offered laparoscopic surgical treatment in recognised endometriosis centres where clinical outcomes are audited.

- Future studies should randomise between laparoscopic surgery and non-surgical therapy incorporating health economic analyses and compare different laparoscopic surgical interventions for treating rectovaginal endometriosis.

**Copyright statement**



**Competing interests:**

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: support from the British Society for Gynaecological Endoscopy (BSGE) for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. All authors with the exception of TC are members of the BSGE.

**Contributorship statement**

The contributorship of the authors is as follows: Mr Dominic Byrne maintained and upgraded the endometriosis database, designed the study and analysis, provided data, contributed to data interpretation and drafting of the manuscript. Dr Tamara Curnow - conducted the statistical analysis, data interpretation and contributed to drafting of the manuscript. Mr Paul Smith

designed the study, conducted literature and reference review and contributed to drafting of the manuscript. Mr Ertan Saridogan – provided data, contributed to data interpretation and drafting of the manuscript. Mr Alfred Cutner – Responsible for set up of the BSGE endometriosis centres project, provided data, contributed to data interpretation and drafting of the manuscript. Professor T. Justin Clark – chaired the BSGE Endometriosis Centres Scientific Advisory Group, designed the study, contributed to data interpretation and drafting of the manuscript and is the Guarantor on behalf of the BSGE Endometriosis centres research group

**Ethics:**

All patients gave written consent to have their data stored on the BSGE database and for its subsequent use in scientific research and publication. Written consent was obtained each time symptoms and quality of life data were collected. The database is managed in accordance with the data protection act, data are encrypted and the database is hosted by a third party that is paid by the BSGE for this service. The BSGE designed and developed the database. The BSGE is a charity which raises funds from its membership and scientific meeting sponsorship. All hopsitals where clinicians enter data are informed in writing by the BSGE to the CEO and Medical Director about the patient data storage on the BSGE endometriosis database to ensure their agreement. Two authors were funded to carry out initial research (PS) and to perform statistical analaysis on the data (TC).

**STROBE checklist:**

The checkilist has been attached and uploaded as a supplemental file to the submitted paper. We have paid particular attention to items which ask authors to "explain the scientific

background and rationale for the investigation being reported" and "state specific objectives, including any prespecified hypotheses."

**Study funding:**

The BSGE is a registered charity and paid for the development and maintenance of the Endometriosis database. The BSGE provided limited funding for one author to perform background research and literature review (PS) and one author (TC) to undertake statistical analysis

**Study sponsor / funder role:**

Each hospital that contributed data acted as a study sponsor in that they agreed to collection of data from their respective endometriosis centre and it being stored on the BSGE endometriosis database for research.

**Statement of the independence of researchers from funders:**

There was no direct research funding apart from the BSGE financial support to set up and administer the database, employ a statistician and a research fellow

**Authors statement:**

We confirm that all authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

**Transparency declaration:**

I, T Justin Clark, on behalf of all other named authors affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

**Data sharing statement:**

The full dataset is available from the corresponding author at t.j.clark@doctors.org.uk

**Study registration number and name of register for any study type:**

Not registered. The BSGE website describes the endometriosis centres project and the establishment of the endometriosis patient registry (endometriosis database) which meets the standards set by NICE for such records.

**Aknowledgements**

We are grateful to Jeremy Wright and Adam Moors who designed and established the BSGE endometriosis database and Dominic Byrne who upgraded it to increase completeness of data collection and follow up.

We are grateful to the BSGE Scientific Advisory Group who approve research on BSGE endometriosis database data and have scrutinised the manuscript. The members are: Prof Justin Clark (chair), Dominic Byrne, Oliver Chappatte, Alfred Cutner, Chris Guyer, Ertan Saridogan and Robert Richardson.

We would like to thank and acknowledge all the BSGE Endocentre teams for contributing to this work by entering their data on the BSGE Endometriosis database, they are listed alphabetically below with number of cases in brackets and name of lead Gynaecologist. The seven centres referred to in the paper with best follow up are marked in bold.

Aberdeen (99) Lucky Saraswat, **ACEMIG (140) Shaheen Khazali**, Altnergavin (36) Iris Menninger, Birmingham (58) Yousri Afifi, Castle Hill (103) Kevin Phillips, CEMIG (199) Saikat Banerjee, Chelsea and Westminster (258) Robert Richardson, Chester (88) Jeremy Hawe, Colchester (81) Barry Whitlow, **Cornwall (257) Dominic Byrne**, Croydon University hospital (57) Emmanuel Ofuasia Dewsbury/Elland (121) Ashwini Trehan, Dorset (57) Tyrone Carpenter, Endometriosis CaRe Oxford (164) Christian Becker, Exeter (23) James Clark, Exppect Edinburgh (52) Stuart Jack, **Guy's and Thomas' (29) Kumar Kunde** Gynaecology.co (98) Alfred Cutner, Homerton (21) Chris Barnick, Imperial (75) Alan Farthing, James Cook Hospital (111) Graham Phillips, Kings College (132) John Bidmead, Lancashire women's and newborn (31) Mohamed Abdel-Aty, Liverpool women's (85) George Botros, Luton and Dunstable (35) Marlin Mubarak, , Mid Yorks (46) Christian Kremer, Norfolk and Norwich University Hospital (53) Edward Morris, North Middlesex (34) Stanley Okolo, **North west pelvic pain, Manchester (87) Edmond Edi-Osagi**, Northwick Park Hospital (81) Kamel Shehata-Iskander, Penine (63) Gaity Ahmad, Plymouth (53) Jonathan Frappell, **Preston Royal, Lancashire (31)**

**Brice Rodriguez**, , Queens University Hospital, Romford (27) Yemi Coker, Royal London (55) Elizabeth Ball, Royal Stoke (69) Gourab Misra, Southampton (160) Adam Moors, , Southmead(104) Sanjay Vyas, St Georges (46) Thomas Ind, St Mary's, Portsmouth (143) Chris Guyer, **St Michaels Hospital, Bristol (81) Caroline Overton**, Stockport (60) Suku George, The northern endometriosis team (49) Tony Chalhoub, Tunbridge Wells (146) Oliver Chappatte, University College London Hospital (302) Ertan Saridogan, University Hospital of Wales (80) Richard Penketh, UPMC Beacon (32) Moiad Alazzam, Whipps Cross Hospital (82) Funlayo Odejinmi, Winchester (21) Keith Louden, Wirral University Teaching Hospital (324) David Rowlands, **Worcestershire (82) Jon Hughes**.

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**Table 1.** Patient reported symptoms prior to laparoscopic surgical excision of rectovaginal endometriosis and at six months, one year and two years post treatment (median scores are presented (0-10 for the first nine symptoms and 0-4 for the remaining 5 symptoms) with total number of patients in brackets).

| Pre menstrual pain | Pre-surgery | 6 months | 12 months | 24 months | Short – term[1] (baseline vs. 6 months) | Long – term[1] (baseline vs. 24 months) | Change[2] (6 months vs. 24 months) |
|---|---|---|---|---|---|---|---|
| Premenstrual pain | 7.0 (4035) | 3.0 (1908) | 3.0 (1177) | 3.0 (558) | 0.000v (1874) | 0.000v (554) | 0.000^ (380) |
| Menstrual pain | 9.0 (4039) | 4.0 (1899) | 4.0 (1171) | 5.0 (551) | 0.000v (1869) | 0.000v (549) | 0.005^ (375) |
| Non cyclical pelvic pain | 6.0 (4154) | 2.0 (2170) | 2.0 (1360) | 3.0 (658) | 0.000v (2160) | 0.000v (656) | 0.000^ (453) |
| Deep dyspareunia | 5.5 (3986) | 1.0 (1998) | 1.0 (1247) | 2.0 (608) | 0.000v (1952) | 0.000v (598) | 0.000^ (403) |
| Cyclical dyschezia | 6.0 (4040) | 0.0 (1937) | 1.0 (1219) | 2.0 (569) | 0.000v (1900) | 0.000v (568) | 0.000^ (384) |
| Non cyclical dyschezia | 3.0 (4135) | 0.0 (2178) | 0.0 (1374) | 0.0 (655) | 0.000v (2162) | 0.000v (646) | 0.000^ (449) |
| Lower back pain | 6.0 (4150) | 3.0 (2188) | 3.0 (1376) | 3.0 (660) | 0.000v (2172) | 0.000v (656) | 0.027^ (457) |
| Bladder pain or pain passing urine | 0.0 (4084) | 0.0 (2162) | 0.0 (1369) | 0.0 (652) | 0.000v (2122) | 0.000v (638) | 0.034^ (446) |
| Difficulty emptying bladder | 0.0 (4002) | 0.0 (2135) | 0.0 (1360) | 0.0 (650) | 0.000v (2075) | 0.105 (628) | 0.002^ (440) |
| Frequent bowel movements | 2.0 (3995) | 2.0 (2154) | 2.0 (1372) | 2.0 (660) | 0.000v (2087) | 0.012v (626) | 0.051 (451) |
| Urgent bowel movements | 1.0 (3996) | 1.0 (2154) | 1.0 (1371) | 1.0 (658) | 0.000v (2091) | 0.006v (623) | 0.000^ (449) |
| Incomplete emptying sensation | 1.0 (3980) | 1.0 (2149) | 1.0 (1372) | 1.0 (659) | 0.000v (2075) | 0.000v (623) | 0.004^ (447) |
| Constipation | 2.0 (4000) | 1.0 (2156) | 1.0 (1368) | 1.0 (658) | 0.000v (2091) | 0.002v (628) | 0.001^ (449) |
| Blood in the stool | 0.0 (3893) | 0.0 (1912) | 0.0 (1206) | 0.0 (546) | 0.000v (1831) | 0.038v (507) | 0.001^ (350) |

Lower score denotes less severe symptoms. Denominator (responses) shown in parentheses

[1] Statistical comparison (Mann Whitney U test) of short term symptom scores (6 months post surgery) and long term symptom scores (2 years post surgery) with baseline scores (pre-surgery)
[2] Statistical comparison (Mann Whitney U test) of change in symptom scores over time post treatment (between 6 months and 2 years)
^ = statistically significant increase, v = statistically significant decrease.
Note that there is some variation in total number of responses depending on whether patients chose not to answer some questions

**Table 2.** Median scores for patient reported quality of life prior to treatment and at six months, one year and two years post treatment with total number of patients in brackets. Median EQVAS lies in the range 0-100 with a higher score associated with a better quality of life. The other median scores (EQ5D) lie in the range 0-2 where a lower score is associated with a better quality of life.

| **Pre menstrual pain** | **Pre-surgery** | **6 months** | **12 months** | **24 months** | **Short – term[2] (baseline vs. 6 months)** | **Long – term[2] (baseline vs. 24 months)** | **Change[3] (6 months vs. 24 months)** |
|---|---|---|---|---|---|---|---|
| EQVAS numeric[1] | 55.0 (4014) | 80.0 (2050) | 80.0 (1247) | 76.0 (575) | 0.000^ (2045) | 0.000^ (573) | 0.024v (396) |
| EQ5D Usual Activities | 1.0 (4004) | 0.0 (2051) | 0.0 (1250) | 0.0 (574) | 0.000v (2042) | 0.000v (570) | 0.477 (395) |
| EQ5D Pain discomfort | 1.0 (4003) | 1.0 (2050) | 1.0 (1252) | 1.0 (573) | 0.000v (2041) | 0.000v (569) | 0.427 (394) |
| EQ5D Anxiety depression | 1.0 (3990) | 0.0 (2049) | 0.0 (1252) | 0.0 (573) | 0.000v (2033) | 0.000v (569) | 0.331 (395) |
| EQ5D Mobility | 0.0 (3998) | 0.0 (2046) | 0.0 (1250) | 0.0 (569) | 0.000v (2035) | 0.000v (563) | 0.339 (392) |
| EQ5D SelfCare | 0.0 (3993) | 0.0 (2033) | 0.0 (1248) | 0.0 (558) | 0.000v (2020) | 0.001v (548) | 0.364 (384) |

Denominator (responses) shown in parentheses

[1]A high Euroqol Visual Analogue Scale (EQ-VAS) score is associated with an improvement in QoL whereas with all other QoL and symptom scores a low value is associated with improvement.
[2] Statistical comparison (Mann Whitney U test ) of short term symptom scores (6 months post surgery) and long term symptom scores (2 years post surgery) with baseline scores (pre-surgery)
[3] Statistical comparison (Mann Whitney U test ) of change in symptom scores over time post treatment (between 6 months and 2 years)
^ = statistically significant increase, v = statistically significant decrease.
Note that there is some variation in total number of responses depending on whether patients chose not to answer some questions.

**Table 3.** Analgesia use prior to surgery and at six months, one year and two years post surgery. Percentage of patients using medication with total number of patients in brackets.

| Pre menstrual pain | Pre-surgery | 6 months | 12 months | 24 months | Short – term[1] (baseline vs. 6 months) | Long – term[1] (baseline vs. 24 months) | Change[2] (6 months vs. 24 months) |
|---|---|---|---|---|---|---|---|
| Paracetamol | 76.0% (4118) | 59.8%(1934) | 60.6% (1235) | 61.4% (610) | 0.000v (1915) | 0.000v (604) | 0.001^ (388) |
| NSAID | 69.8% (4099) | 48.9%(1924) | 48.3% (1229) | 52.0% (603) | 0.000v (1903) | 0.000v (593) | 0.013^ (385) |
| Opiates | 28.1% (3953) | 16.1% (1895) | 16.8% (1214) | 16.6% (592) | 0.000v (1859) | 0.000v (575) | 0.006^ (376) |

Denominator (responses) shown in parentheses

NSAID – non-steroidal anti-inflammatory drug

[1] Statistical comparisons of short term symptom scores (6 months post surgery) and long term symptom scores (2 years post surgery) with baseline scores (pre-surgery) assessed using a 2-tailed sign test.
[2] Statistical comparison of change in symptom scores over time post treatment (between 6 months and 2 years) using a 2-tailed sign-test.
^ = statistically significant increase, v = statistically significant decrease.
Note that there is some variation in total number of responses depending on whether patients chose not to answer some questions

**Table 4.** Sensitivity analysis for missing post-operative data.

| | **Short-term (6 months)[1]** | **Long–term (2 years)[1]** | **Range** |
|---|---|---|---|
| *Symptoms* | | | |
| Premenstrual pain | 9 | 8 | [0, 10] |
| Menstrual pain | 10 | 10 | [0, 10] |
| Non cyclical pelvic pain | 7 | 6 | [0, 10] |
| Deep dyspareunia | 8 | 6 | [0, 10] |
| Cyclical dyschezia | 7 | 7 | [0, 10] |
| Non cyclical dyschezia | 5 | 3 | [0, 10] |
| Low back pain | 7 | 7 | [0, 10] |
| Bladder pain | 2 | 1 | [0, 10] |
| Voiding difficulty | 0 | NS | [0, 10] |
| Frequent bowel movements[2] | 3 | 3 | [0, 4] |
| Urgent bowel movements[2] | 2 | 2 | [0, 4] |
| Incomplete bowel movements[2] | 2 | 2 | [0, 4] |
| Constipation[2] | 2 | 2 | [0, 4] |
| Blood in the stool[2] | 0 | 1 | [0, 4] |
| | | | |
| *Quality of life*[2] | | | |
| EQ Visual analogue score | 40 | 55 | [0, 100] |
| EQ5D Usual Activities | 2 | 1 | [0, 2] |
| EQ5D Pain and discomfort | 2 | 2 | [0, 2] |
| EQ5D Anxiety and depression | 1 | 1 | [0, 2] |
| EQ5D Mobility | 1 | 1 | [0, 2] |
| EQ5D Self care | 1 | 1 | [0, 2] |

[1] The worst possible score that could be reported for all the missing post-operative data in order for the short-term (six months) or long-term statistics in Tables 3 & 4 to still be significant (The test statistics that were not significant (NS) to start with have not been included).

[2] A high EuroQol Visual Analogue Scale (EQ-VAS) score is associated with an improvement in QoL whereas with all other QoL and symptom scores a low value is associated with improvement.

**Table 5.** Sensitivity analysis for missing post-operative data restricted to the seven British Society for Gynaecological Endoscopy (BSGE) Endometriosis Centres with the most complete follow-up.

| | **Short-term (6 months)[1]** | **Long–term (2 years)[1]** | **Range** |
|---|---|---|---|
| *Symptoms* | | | |
| Premenstrual pain | 10 | 7 | [0, 10] |
| Menstrual pain | 10 | 9 | [0, 10] |
| Non cyclical pelvic pain | 10 | 5 | [0, 10] |
| Deep dyspareunia | 10 | 5 | [0, 10] |
| Cyclical dyschezia | 10 | 5 | [0, 10] |
| Non cyclical dyschezia | 7 | 4 | [0, 10] |
| Low back pain | 10 | 5 | [0, 10] |
| Bladder pain | 4 | 1 | [0, 10] |
| Voiding difficulty | 1 | NS | [0, 10] |
| Frequent bowel movements[2] | 2 | NS | [0, 4] |
| Urgent bowel movements[2] | 3 | NS | [0, 4] |
| Incomplete bowel movements[2] | 2 | NS | [0, 4] |
| Constipation[2] | 2 | NS | [0, 4] |
| Blood in the stool[2] | 2 | 1 | [0, 4] |
| | | | |
| *Quality of life*[2] | | | |
| EQ Visual analogue score | 0 | 55 | [0, 100] |
| EQ5D Usual Activities | 1 | 1 | [0, 2] |
| EQ5D Pain and discomfort | 2 | 2 | [0, 2] |
| EQ5D Anxiety and depression | 2 | 1 | [0, 2] |
| EQ5D Mobility | 0 | 1 | [0, 2] |
| EQ5D Self care | 1 | NS | [0, 2] |

[1] The worst possible score that could be reported for all the missing post-operative data in order for the short-term (six months) or long-term statistics in Tables 3 & 4 to still be significant (The test statistics that were not significant (NS) to start with have not been included).

[2] A high EuroQol Visual Analogue Scale (EQ-VAS) score is associated with an improvement in QoL whereas with all other QoL and symptom scores a low value is associated with improvement.

**Table 6**. Incidence of peri-operative and post-operative complications.

| Peri-operative complication | Number of patients | Incidence |
|---|---|---|
| | | |
| Haemorrhage >1litre | 43 | 0.9% |
| Ureteric injury | 24 | 0.5% |
| Unexpected bowel injury | 28 | 0.6% |
| Unexpected bladder injury | 17 | 0.4% |
| Unexpected vascular injury | 10 | 0.2% |
| Epigastric injury | 4 | 0.1% |
| Conversion to laparotomy | 41 | 0.9% |
| Colostomy | 9 | 0.2% |
| Ileostomy | 14 | 0.3% |
| Unplanned Removal of any other organ | 11 | 0.2% |
| Death | 0 | 0.0% |
| **Total suffering any perioperative complication** | **220** | **4.7%** |
| | | |
| **Post-operative complication** | | |
| | | |
| Pelvic haematoma | 37 | 0.8% |
| Pelvic Abscess | 17 | 0.4% |
| Urinary tract leak | 11 | 0.2% |
| Bowel leak | 17 | 0.4% |
| Urinary tract fistula | 2 | 0.0% |
| Bowel fistula | 12 | 0.3% |
| Severe sepsis | 10 | 0.2% |
| Pulmonary embolism | 1 | 0.0% |
| **Total suffering any post operative complication** | **120** | **2.5%** |
| | | |

Note that some patients suffered more than one complication

**Table 7.** Incidence of bowel complication related to the type of surgery performed on the bowel.

| Type of bowel surgery | Number of operations | UBI | Leak | Fistula | Total |
|---|---|---|---|---|---|
| No Bowel Surgery | 1740 | 6 (0.3%) | 3 (0.2%) | 2 (0.1%) | 11 (0.6%) |
| Shaved | 2746 | 18 (0.7%) | 6 (0.2%) | 5 (0.2%) | 29 (1.1%) |
| Disc Resection | 54 | 0 (0.0%) | 4 (7.4%) | 3 (5.6%) | 5 (9.3%) |
| Segmental Resection | 181 | 4 (2.2%) | 4 (2.2%) | 2 (1.1%) | 7 (3.9%) |
| Total | 4721 | 28 (0.6%) | 17 (0.4%) | 12 (0.3%) | 52 (1.1%) |

*UBI = unexpected bowel injury at the time of surgery. Leak = any bowel leak identified after primary surgery. Fistula formation is a late complication from surgery.*

**Supplementary table 1.** Patient reported symptoms prior to laparoscopic surgical excision of rectovaginal endometriosis and at six months, one year and two years post treatment (median scores are presented (0-10 for the first nine symptoms and 0-4 for the remaining 5 symptoms) with total number of patients in brackets) restricted to the seven British Society for Gynaecological Endoscopy (BSGE) Endometriosis Centres with the most complete follow-up. A lower score is associated with less severe symptoms.

| | **Pre-surgery** | **6 months** | **12 months** | **24 months** | **Short – term[1] (baseline vs. 6 months)** | **Long – term[1] (baseline vs. 24 months)** | **Change[2] (6 months vs. 24 months)** |
|---|---|---|---|---|---|---|---|
| Premenstrualpain | 7.0 (648) | 2.0 (447) | 3.0 (284) | 4.0 (122) | 0.000v (437) | 0.000v (122) | 0.108 (100) |
| Menstrualpain | 9.0 (649) | 4.0 (446) | 4.0 (284) | 6.0 (121) | 0.000v (437) | 0.000v (121) | 0.017^ (99) |
| Noncyclicalpelvicpain | 6.0 (676) | 2.0 (517) | 2.0 (333) | 3.0 (152) | 0.000v (516) | 0.000v (151) | 0.007^ (125) |
| Deepdyspareunia | 6.0 (646) | 1.0 (453) | 1.0 (303) | 2.0 (137) | 0.000v (449) | 0.000v (136) | 0.317 (105) |
| Cyclicaldyschezia | 6.0 (648) | 0.0 (455) | 0.0 (295) | 3.0 (128) | 0.000v (444) | 0.000v (128) | 0.000^ (103) |
| Noncyclicaldyschezia | 3.0 (673) | 0.0 (519) | 0.0 (339) | 0.0 (151) | 0.000v (516) | 0.000v (149) | 0.192 (123) |
| Lowerbackpain | 6.0 (671) | 2.0 (521) | 2.0 (341) | 4.0 (152) | 0.000v (515) | 0.000v (151) | 0.905 (126) |
| Bladderpainorpainpassingurine | 0.0 (668) | 0.0 (518) | 0.0 (337) | 0.0 (153) | 0.000v (511) | 0.000v (151) | 0.560 (126) |
| Difficultyemptyingbladder | 0.0 (662) | 0.0 (516) | 0.0 (336) | 0.0 (153) | 0.000v (506) | 0.136 (150) | 0.558 (124) |
| Frequentbowelmovements | 2.0 (665) | 2.0 (521) | 2.0 (340) | 2.0 (151) | 0.000v (513) | 0.343 (146) | 0.096 (125) |
| Urgentbowelmovements | 1.0 (665) | 1.0 (521) | 1.0 (339) | 1.0 (150) | 0.000v (513) | 0.524 (145) | 0.000^ (124) |
| Incompleteemptyingsensation | 1.0 (662) | 1.0 (519) | 1.0 (340) | 1.0 (153) | 0.000v (509) | 0.426 (147) | 0.001^ (126) |
| Constipation | 1.0 (664) | 1.0 (521) | 1.0 (340) | 1.0 (151) | 0.000v (512) | 0.093 (146) | 0.024^ (125) |
| Bloodinthestool | 0.0 (641) | 0.0 (450) | 0.0 (294) | 0.0 (125) | 0.000v (439) | 0.019v (118) | 0.074 (98) |

Denominator (responses) shown in parentheses

[1] Statistical comparison (Mann Whitney U test) of short term symptom scores (6 months post surgery) and long term symptom scores (2 years post surgery) with baseline scores (pre-surgery)
[2] Statistical comparison (Mann Whitney U test) of change in symptom scores over time post treatment (between 6 months and 2 years)
^ = statistically significant increase, v = statistically significant decrease.
Note that there is some variation in total number of responses depending on whether patients chose not to answer some question

**Supplementary table 2.** Median scores for patient reported quality of life prior to treatment and at six months, one year and two years post treatment with total number of patients in brackets restricted to the seven British Society for Gynaecological Endoscopy (BSGE) Endometriosis Centres with the most complete follow-up. Median EQVAS lies in the range 0-100 with a higher score associated with a better quality of life. The other median scores (EQ5D) lie in the range 0-2 where a lower score is associated with a better quality of life.

| | **Pre-surgery** | **6 months** | **12 months** | **24 months** | **Short – term[2] (baseline vs. 6 months)** | **Long – term[2] (baseline vs. 24 months)** | **Change[3] (6 months vs. 24 months)** |
|---|---|---|---|---|---|---|---|
| EQUVASnumeric | 55.0 (664) | 80.0 (510) | 80.0 (328) | 75.0 (136) | 0.000^ (508) | 0.000^ (136) | 0.036v (116) |
| EQ5DUsualActivities | 1.0 (666) | 0.0 (510) | 0.0 (330) | 0.0 (135) | 0.000v (510) | 0.000v (135) | 0.140 (116) |
| EQ5DPaindiscomfort | 1.0 (667) | 1.0 (510) | 1.0 (332) | 1.0 (135) | 0.000v (510) | 0.000v (135) | 0.025^ (116) |
| EQ5DAnxietydepression | 1.0 (663) | 0.0 (510) | 0.0 (332) | 0.0 (134) | 0.000v (507) | 0.000v (134) | 0.490 (116) |
| EQ5DMobility | 0.0 (667) | 0.0 (510) | 0.0 (332) | 0.0 (134) | 0.000v (510) | 0.000v (134) | 0.034^ (116) |
| EQ5DSelfCare | 0.0 (666) | 0.0 (509) | 0.0 (332) | 0.0 (135) | 0.000v (508) | 0.134 (135) | 0.453 (116) |

Denominator (responses) shown in parentheses

[1]A high Euroqol Visual Analogue Scale (EQ-VAS) score is associated with an improvement in QoL whereas with all other QoL and symptom scores a low value is associated with improvement.
[2] Statistical comparison (Mann Whitney U test ) of short term symptom scores (6 months post surgery) and long term symptom scores (2 years post surgery) with baseline scores (pre-surgery)
[3] Statistical comparison (Mann Whitney U test ) of change in symptom scores over time post treatment (between 6 months and 2 years)
^ = statistically significant increase, v = statistically significant decrease.
Note that there is some variation in total number of responses depending on whether patients chose not to answer some questions.

**Supplementary table 3.** Analgesia use prior to surgery and at six months, one year and two years post surgery restricted to the seven British Society for Gynaecological Endoscopy (BSGE) Endometriosis Centres with the most complete follow-up. Percentage of patients using medication with total number of patients in brackets.

| | Pre-surgery | 6 months | 12 months | 24 months | Short – term[1] (baseline vs. 6 months) | Long – term[1] (baseline vs. 24 months) | Change[2] (6 months vs. 24 months) |
|---|---|---|---|---|---|---|---|
| Paracetamol | 68.3% (672) | 51.1% (464) | 50.3% (302) | 56.3% (144) | 0.000v (461) | 0.002v (142) | 0.031^ (100) |
| NSAID | 74.0% (672) | 48.0% (465) | 47.0% (302) | 59.0% (144) | 0.000v (462) | 0.053 (142) | 0.003^ (100) |
| Opiates | 27.2% (669) | 16.6% (465) | 16.9% (301) | 25.7% (144) | 0.000v (462) | 0.418 (142) | 0.001^ (100) |

Denominator (responses) shown in parentheses

NSAID – non-steroidal anti-inflammatory drug

[1] Statistical comparisons of short term symptom scores (6 months post surgery) and long term symptom scores (2 years post surgery) with baseline scores (pre-surgery) assessed using a 2-tailed sign test.
[2] Statistical comparison of change in symptom scores over time post treatment (between 6 months and 2 years) using a 2-tailed sign-test.
^ = statistically significant increase, v = statistically significant decrease.
Note that there is some variation in total number of responses depending on whether patients chose not to answer some questions

STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No | Recommendation |
|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract **Page 1** |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Pages 2-3** |
| **Introduction** | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported **Pages 4-5** |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses **Page 5** |
| **Methods** | | |
| Study design | 4 | Present key elements of study design early in the paper **Page 5** |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page 5** |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Pages 5-6**<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Pages 6-8** |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Pages 6-8** |
| Bias | 9 | Describe any efforts to address potential sources of bias **Pages 8-9** |
| Study size | 10 | Explain how the study size was arrived at **Not done – largest prospective cohort in the world by far – decision to analyse and publish once large number obtained - 5000; Not a trial so no formal sample size calculation** |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Pages 6-8** |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding **Pages 8-9** |
| | | (*b*) Describe any methods used to examine subgroups and interactions **Pages 8-9** |
| | | (*c*) Explain how missing data were addressed **Pages 8-9** |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **Pages 8-9**<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of |

sampling strategy

(*e*) Describe any sensitivity analyses **Pages 8-9**

Continued on next page

| | | |
|---|---|---|
| **Results** | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Page 9** |
| | | (b) Give reasons for non-participation at each stage **Not done - LTFU presented** |
| | | (c) Consider use of a flow diagram **Not done – not an RCT or controlled study** |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Page 9-11** |
| | | (b) Indicate number of participants with missing data for each variable of interest **Each variable as number of participants** |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **Table 2-4** |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time **Table 1-4** |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Page 9-11** |
| | | (*b*) Report category boundaries when continuous variables were categorized **Not applicable** |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **Not applicable** |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **Page 12, Table 5** |
| **Discussion** | | |
| Key results | 18 | Summarise key results with reference to study objectives **Pages 13 and 20** |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Pages 13-15** |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Pages 15-16** |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results **Pages 16-17** |
| **Other information** | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Page 23** |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

# Laparoscopic excision of deep rectovaginal endometriosis in BSGE Endometriosis Centres: A multicentre prospective cohort study

| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2017-018924.R1 |
| Article Type: | Research |
| Date Submitted by the Author: | 10-Nov-2017 |
| Complete List of Authors: | Byrne, Dominic ; Royal Cornwall Hospitals Trust, Truro, Cornwall , Gynaecology<br>Curnow, Tamara; Bodriggy Health Centre, Hayle, Cornwall.<br>Smith, Paul; University of Birmingham,<br>Cutner, Alfred; University College London Hospitals, Gynaecology<br>Saridogan, Ertan; University College London Hospitals, Gynaecology<br>Clark, T; Birmingham Women's NHS Foundation Trust, Gynaecology; University of Birmingham, |
| Primary Subject Heading: | Obstetrics and gynaecology |
| Secondary Subject Heading: | Obstetrics and gynaecology |
| Keywords: | Laparoscopy, bowel endometriosis, deep infiltrating endometriosis, rectal endometriosis, rectovaginal endometriosis |
| | |

**Title**

# Laparoscopic excision of deep rectovaginal endometriosis in BSGE Endometriosis Centres: A multicentre prospective cohort study

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**Abstract**

Objective**:** To estimate the effectiveness and safety of laparoscopic surgical excision of rectovaginal endometriosis.

Design**:** A multicentre, prospective cohort study

Setting**:** 51 hospitals accredited as specialist Endometriosis Centres.

Participants**:** 5,162 women of reproductive age with rectovaginal endometriosis of which 4,721 women had planned laparoscopic excision.

Interventions**:** Laparoscopic surgical excision of rectovaginal endometriosis requiring dissection of the para-rectal space.

Main outcome measures: Standardised symptom questionnaires enquiring about chronic pelvic pain, bladder and bowel symptoms, analgesia use and quality of life (EuroQol) completed prior to surgery and at 6, 12 and 24 months post-operatively. Serious peri- and post-operative complications including major haemorrhage, infection and visceral injury were recorded.

Results: At 6 months post surgery there were significant reductions in premenstrual, menstrual and non-cyclical pelvic pain, deep dyspareunia, dyschezia, low back pain and bladder pain. In addition, there were significant reductions in voiding difficulty, bowel frequency, urgency, incomplete emptying, constipation and passing blood. These reductions were maintained at two years, with the exception of voiding difficulty. Global quality of life significantly improved from a median pre-treatment score of 55/100 to 80/100 at six months. There was a significant improvement in quality of life in all measured domains and in quality-adjusted life-years. These improvements were sustained at two years. All analgesia use was reduced and in particular opiate use fell from 28.1% prior to surgery to 16.1% at six months. The overall incidence of complications was 6.8% (321/4721). Gastrointestinal

complications (enterotomy, anastomotic leak or fistula) occurred in 52 (1.1%) operations and of the urinary tract (ureteric / bladder injury or leak) in 49 (1.0%) procedures.

Conclusion: Laparoscopic surgical excision of rectovaginal endometriosis appears to be effective in treating pelvic pain and bowel symptoms and improving health-related quality of life and has a low rate of major complications when performed in specialist centres.

Keywords: Laparoscopy; bowel endometriosis; deep infiltrating endometriosis; rectal endometriosis; rectovaginal endometriosis

**Article summary – Strengths and limitations**

- Our study is by far the largest , multcentre observational cohort published for the laparoscopic surgical treatment of rectovaginal endometriosis with a sample of nearly 5000 cases.
- Data were prospectively collected, minimising missing data and recall bias, were obtained from multiple centres enhancing transferability, and outcomes measurements were patient reported reducing interpreter bias.
- Efficacy outcomes were assessed in both the short term (at six months) and longer term (at two years) following surgery. In addition, the scale of these data and the method of collection have enabled a robust assessment of the risk of complications from this type of surgery. The reported incidence of complications cannot however, be used as indicative risk for patients who have care given in non-specialist endometriosis centres.
- The main limitation of our study relates to missing data from incomplete data entry, incomplete follow-up or uncompleted follow up at closure of the study. We performed sensitivity analyses to explore the robustness of our results to incompleteness. The results were stable, remaining significant in some cases even when symptomatic outcomes for those women with missing data were assumed to be the worst possible outcome.
- Historical control data were used from the same patients prior to surgical intervention although the study would have benefited from a non-surgically treated control group. However, persuading a group of women with severe, refractory symptoms to continue with non-surgical treatment would be challenging.

## Introduction

Endometriosis is a common and serious problem for women in their reproductive years and can cause chronic pelvic pain, subfertility, bowel and urinary dysfunction.[1] The associated morbidity places a substantial economic burden on society as a result of direct healthcare costs and indirect productivity losses. In the USA, direct healthcare costs have been estimated to be $2,801 annually per patient with an additional cost of $1,023 annually per patient due to loss of productivity. Overall the costs associated with endometriosis in the USA are estimated at 22 billion dollars per annum.[2]

Deep endometriosis in the posterior pelvis frequently affects the space between the anterior wall of the rectosigmoid and the posterior vaginal wall and is usually referred to as rectovaginal endometriosis. There is limited evidence supporting the sustained effectiveness and acceptability of medical therapies in improving the symptoms of rectovaginal endometriosis.[3–5] Consequently surgical treatment has been proposed to completely excise the deep rectovaginal disease.[6–8]

Advances in instrumentation and surgical experience have led to laparoscopic treatment superseding alternative surgical routes such as laparotomy and transvaginal excision. Previous studies have reported improvements in generic quality of life data following surgical excision of endometriosis involving the bowel, but these evaluations have been undertaken using small cohorts of women usually from single centres, affecting the precision and generalisability of the derived results.[9–11] Whilst these findings of improved symptomatic outcomes are promising, it is well recognised that surgery for deep endometriosis with bowel involvement is complex and can be associated with serious and potentially life threatening complications.[10] For these reasons, the ESHRE Guidelines on the 'Management of women with endometriosis' recommend that clinicians refer women with suspected or diagnosed

deep endometriosis to a centre of expertise that offers all available treatments in a multidisciplinary context.[1]

In 2006 the British Society for Gynaecological Endoscopy (BSGE) developed specialist endometriosis centres (Endocentres), where patients would be treated by surgeons who work in multidisciplinary teams, audit their outcomes and perform sufficient workload to maintain their surgical skills.[12]

In view of the paucity of world literature data pertaining to the effectiveness and safety of this highly complex surgery for a common gynaecological condition, we undertook a prospective, multi-centre cohort study to estimate (i) effectiveness of surgery on patient reported symptoms associated with endometriosis as well as its impact upon women's health related quality of life and (ii) safety by examining rates of surgical complications using data collected from the BSGE Endocentres dataset.

## Methods

### *Study design*

A multicentre prospective cohort study of pre-menopausal women undergoing surgery for pelvic pain associated with rectovaginal disease resistant to medical treatment or conservative surgical therapy was performed. Standardised diagnostic, operative, histological and patient outcome data were prospectively collected from 51 BSGE Endometriosis centres between 1st January 2009 and 30th June 2016.

### *Study population*

Women treated in a BSGE Endocentre who underwent laparoscopic excision of deep rectovaginal endometriosis, which required dissection of the pararectal space and gave written consent for data collection were included in the study. Dissection of the pararectal

space was chosen as the inclusion criterion for cases to be studied because access to this anatomical space is necessary to free adherent bowel prior to excision of deep rectovaginal disease. Furthermore, this operative step is necessary irrespective of the type of surgery performed on the bowel. So by choosing this step of the surgical procedure the BSGE could be assured that all cases of deep rectovaginal endometriosis would be included reducing the risk of selection bias. Clear explanation of dissection of the deep pararectal space is provided on the BSGE endometriosis database for surgeons. Whilst there have been a number of historical scoring systems for endometriosis, some were not developed prior to the inception of the BSGE project and none have been universally accepted.[13–16] In order to retain accreditation as a BSGE Endocentre, all consenting patients who undergo surgery for deep rectovaginal endometriosis that includes dissection of the pararectal space in an Endocentre must have their data entered on to the BSGE national endometriosis database.

*Clinical data*

Standardised patient symptom data and quality of life (QoL) assessments were collected prior to surgery as a baseline control. The assessments were repeated at six months, one year and two years after surgery. To ensure consistent timing of follow-up, the database only accepts post-operative data entry within an interval from four weeks before the exact date required and up to eight weeks after the exact date.

All patients recorded their clinical symptoms on a BSGE standard questionnaire using a 0-10 point Likert scale for premenstrual pain, menstrual pain, non cyclical pelvic pain, deep dyspareunia, cyclical dyschezia, non cyclical dyschezia, lower back pain, bladder pain and voiding difficulty. In addition, patients recorded details of bowel function with graded answers for; frequency of bowel movement, urgency of bowel movement, incomplete empyting sensation, constipation and blood in the stool. Patient reported quality of life data were collected using EuroQol 5D-3L questionnaire and EuroQuol Visual Analogue Score.[17,18] The five domains of the EuroQol 5D-3L questionnaire were combined to compute a single weighted index score (a more sensitive measure of quality of life) using the standard

UK time trade-off health-state valuation[19] (as used by NICE for assessing quality-adjusted life years (QALYs)) . In this EQ5d index score 1 represents full health and 0 represents death. There are some health states that are assigned negative values (i.e. worse than death).

Dichotomous data ('yes or 'no') were collected for use of analgesia (parcetamol, non steroidal anti-inflammatory drug (NSAID) or opiates) and medical therapy (oral contraceptive pill, Mirena Intrauterine system™ (Bayer, Germany), GNRH analogues alone, GNRH analogues plus add back hormone replacement, systemic progestogens or aromatase inhibitors).

*Surgical data*

Details of previous endometriosis surgery were recorded including adnexal surgery and hysterectomy. Surgical details were collected using a standard dataset describing the name and level of the surgeon, whether a colorectal and/or a urological surgeon also undertook the surgery and whether the surgery was laparoscopic or laparotomic. The distribution of any endometriosis deposits was described by 'yes' or 'no', for right and left pelvic side-wall, right and left endometrioma, right and left uterosacral ligament and obliteration of the pouch of Douglas. Bowel involvement of endometriosis was also recorded dichotomously for 'rectal involvement', 'rectovaginal nodule', or involvement of 'appendix', 'small bowel' and 'rectosigmoid'. Co-existent bladder endometriosis was recorded by yes or no for superficial bladder, deep bladder and deep utero-vesical endometriosis.

The surgeon recorded the surgical procedure for each of the above areas of distribution of endometriosis from a list of; 'ablated', 'excised', 'ablated and excised', 'not treated' or 'not present'. Surgery on any endometrioma present was recorded by selecting from a list of; 'ablated', 'excised', 'oophorectomy', 'drained only', 'not treated' or 'not applicable'. Pararectal space dissected was recorded as yes or no. Surgery on a rectovaginal nodule was recorded as 'ablated', 'excised', 'not treated' or 'not applicable'. Opening of the vagina

as part of the surgery was recorded as 'yes', 'no' or 'not applicable'. The type of bowel surgery was recorded by selecting from a list of; 'not applicable', 'not treated', 'shaved', 'disc resection' or 'segmental resection', along with whether a stoma was formed, or not. Surgery on any bladder endometriosis was recorded as; 'ablated', 'excised without bladder opening', 'excised with bladder opening', 'not present' or 'not treated'. Ureteric endometriosis surgery was described by ureteric nodule excised (yes, no or not present), right ureterolysis (yes, no or not applicable), left ureterolysis (yes, no or not applicable), JJ stent (yes or no). Finally, data were collected regarding performance of a concomitant hysterectomy (yes, no or not applicable) with space for free text.

Recording of complications was divided into two sections with 'yes' or 'no' answers for a standardised list of perioperative and post operative complications. Complication data included surgical injury to urological, gastrointestinal or vascular structures, unplanned procedures including conversion to laparotomy, infective morbidity, pulmonary embolism and death. Histology of removed specimens was examined for malignant transformation.

*Statistical Methods*

Data were analysed according to the study eligibility critera, namely: a valid operation date was entered, the intended operation was via a laparoscopy, the para-rectal space was dissected and there was excision of endometriosis. If duplicate data were present, the most complete dataset was used. Centres which entered fewer than 20 cases in the total study period were excluded.

Non-numerical scores (eg: bowel symptoms) and the EuroQuol 5D-3L were coded numerically with an assumed underlying interval scale. Median scores were computed along with the 95% confidence interval about the median.

For the patient reported data, pair-wise comparisons were made using the baseline pre-operative data as a control. Data were thus only included if both the pre-operative and the relevant post-operative data were entered. We also compared the symptom scores at six

months with those at two years to assess the post-operative trend. The Mann Whitney U test (Wilcoxon rank sum) was used for comparison for data with more than two outcomes and the sign test for dichotomous data. A statistic was considered significant if the probability of it occurring by chance was <0.05 on a two-tailed test.

As post-operative follow-up was incomplete, the impact of this was assessed in two ways. The first method was by restricting the analysis to centres with more complete follow-up; defined as centres performing at least 50 operations in the study period,with more than 90% of pre-operative questionnaires and more than 70% of post-operative questionnaires entered onto the BSGE database for at least one post-operative clinical follow-up period. The second method was to include all women for whom a pre-operative, baseline score was present. If the post-operative results were reported then these were used. If the post-operative results were not present then an assigned score was used. . The assigned score was the same for all patients with missing post-operative data. The assigned score was initially the best outcome possible and was then changed stepwise through less desirable outcomes. With each assigned value the significance calculation was repeated. The last value of the assigned score at which the outcome is still significant gives a measure of the sensitivity of the result to the missing data. If, for example, the statistic is still significant with the worst possible outcome assigned to the missing post-operative dataset then the outcome is effectively independent of the missing responses.

The data analysis was performed using Matlab (MathWorks) version R2011b.

## Results

In BSGE Endocentres between 1st Jan 2009 and 30th June 2016, 5,162 women underwent surgery for deep rectovaginal endometriosis, which included dissection of the pararectal space. Women who underwent planned laparotomy (160; 3.1%), only had ablative

treatment of their endometriosis (100; 1.9%), or had no treatment of their endometriosis (181; 3.5%) were excluded from further analysis. Thus a total of 4,721 women had planned laparoscopic excision of deep rectovaginal endometriosis in a total of 51 Endocentres. Previous surgery for endometriosis had been performed in 55.1% (2,602) of these women, with 7.0% (333) having had one ovary removed, 3.0% (141) both ovaries removed and 5.0% (234) having had a hysterectomy. The median age of women having surgery was 35.1 years ($90^{th}$ centile range 25.9 - 44.8 years).

*Surgical findings and procedures*

At surgery endometriosis was identified on the left pelvic side wall in 69.0% (3,259) patients and on the right side wall in 57.7% (2,726). It was on the left uterosacral ligament in 78.4% (3,702) patients and the right uterosacral ligament in 70.8% (3,341). The pouch of Douglas was obliterated in 67.1% (3,167) women and a rectovaginal nodule present in 68.6% (3,238) women. There was endometriosis present on the rectum in 54.7% (2,582) women, the caecum in 1.3% (60) women, the appendix in 2.3% (110) women, small bowel in 1.6% (75) women and rectosigmoid in 18.1% (856) women. Deep uterovesical disease was present in 422 women (8.9%).

Gonadatrophin releasing hormone agonists were given to 23.0% (1087) women prior to surgery. The operation was undertaken by a senior gynaecologist in 96.4% (4,549) cases and a colorectal surgeon was present in 27.6% (1,304) cases and a urologist in 320 (6.8%) cases. Pararectal dissection was performed in all cases and ureterolysis on the left in 65.5% (3,092) and on the right in 57.1% (2,695) cases. A ureteric nodule of endometriosis was excised in 9.0% (424) and JJ ureteric stents used in 9.2% (434) cases. Bowel surgery was performed in 63.1% (2,981) cases and 1.3% (62) women had a stoma. A hysterectomy was performed in 723 (15.3%) women. Conversion to laparotomy occurred in 41 (0.9%) cases. There were no cases of malignancy in any of the endometriosis specimens.

*Follow up performance*

Whilst preoperative data were expected in 4,721 women, symptom data were available for 4,210 (89%) and QoL data for 4,041 (86%) women. At six months follow up symptom scores were available in 2,350 (50%) and QoL scores in 2241 (47%) of women. At one year post operation, data were expected for 3,977 women, of whom symptom data were present in 1499 (38%) and QoL in 1380 (35%). At two years symptom data were present in 729 (27%) and QoL data in 644 (24%) out of a possible 2,704 women.

In the seven endocentres with most complete follow up; preoperative symptom data were available for 684 (97%) of the 707 women and QoL data for 668 (94%) women. At six months symptom data were present for 537 (76%) and QoL data for 530 (75%) women. At one year post surgery, data were expected from 553 women and symptom data were present in 356 (64%) and QoL in 347 (63%) women. At two years post operation data were expected in 319 women and symptom data were present for 160 (50%) and QoL data in 145 (45%) women.

*Symptom outcomes*

At six months after laparoscopic excision of endometriosis there was a significant reduction in pain scores for premenstrual pain (from a median of 7/10 to 3/10), menstrual pain (from 9/10 to 5/10) and non cyclical pelvic pain (from 6/10 to 2/10) when compared to pre-operative scores. A significant reduction in pain scores also occurred for deep dyspareunia (from 6/10 to 1/10), cyclical (6/10 to 1/10) and non-cyclical dyschezia (3/10 to 0/10), low back pain (6/10 to 3/10) and a statistically significant drop in bladder pain although no change in the median score. In addition, there was a statistically significant (although not clinically significant) reduction in voiding difficulty, bladder pain, bowel frequency, bowel urgency, incomplete bowel emptying, constipation and passing blood in the stool (see table 1).

The same statistically significant reduction in symptoms remained present at two years post surgery for all symptoms except voiding difficulty. A comparison of the symptoms at six

months was made with the symptoms at two years in order to assess the post-operative trend in symptom scores. This showed that there was a statistically significant but clinically small increase in all symptoms except voiding difficulty over the 18 months (see table 1).

The median global QoL on a 100 point visual analogue scale improved from 55 pre-operatively to 80 post-operatively. There was no statistically significant degradation in effect between 6 and 24 months in all measured QoL domains with the exception of the visual analogue score, which showed a statistically significant (although clinically negligible) lessening over this timeframe (see table 2, median score dropped from 80/100 to 76/100). Patient reported QoL for all five domains of the EuroQol questionnaire showed a statistically significant improvement in QoL at six months post surgery that was sustained at two years post surgery. These five domains are combined to give a single weighted index score (EQ5D index) which can be used as a measure of quality-adjusted life years. This more sensitive measure showed a clinically significant improvement (from a mean of 0.525 to 0.756) at 6 months post surgery that was sustained at two years (0.751).

Analgesia use was significantly reduced at six and 24 months post surgery compared to pre-operative levels for all three analgesic types. Paracetamol use dropped from 76.0% patients to 59.8% at 6 months, NSAID use dropped from 69.8% patients to 48.9% at 6 months and opiate use dropped from 28.1% patients to 16.1% at 6 months.There was however a statistically significant (although clinically small) increase in paracetamol, NSAID and opiate use between six and 24 months post-operatively (see table 3).

*Sensitivity analyses*

Sensitivity analysis on the reduction of patient reported symptoms and the improvement in quality of life post surgery was used to estimate the effect of incomplete data on the significance of the results and is shown in table 4. For all symptoms except voiding difficulty, constipation and blood in the stool, the median scores for missing post-operative data at 6 months would have to be higher (worse) than at baseline for change in scores to become

statistically non-significant. Indeed, menstrual pain scores at six months remained significantly improved on the pre-operative scores even if all the missing six month scores are assumed to be 10 (maximum pain). To further test the robustness of the data to missing values, data from the seven centres with the best follow-up were analysed separately (see table 5, supplementary tables 1-3). Improvement in premenstrual pain, menstrual pain, non-cyclical pelvic pain, deep dyspareunia, cyclical dyschezia, lower back pain, EQ-VAS and EQ5D index were all statistically significant even if the missing data scores were of the worst possible outcome.

*Surgical complications*

The overall incidence of complications was 6.8% (321), with perioperative complications in 4.7% (220) operations and late operative complications in 2.5% (120) women, including 19 women suffering both peri, and postoperative complications (see table 6). Bowel complications occurred in 1.1% (52 operations) and the incidence varied according to whether bowel surgery was undertaken and if so, what type of procedure; 0.6% (11) where no coexistent bowel surgery was undertaken, 1.1% (29), with bowel shaving, 9.3% (5) with disc resection and 3.9% (7) with segmental bowel resection (see table 7).

## Discussion

*Statement of principal findings*

Laparoscopic excision of severe rectovaginal endometriosis, performed in specialist centres in women with chronic pelvic pain, was associated with significant reduction in pain symptoms and improved health related quality of life. Moreover, the reduction in pain and increased quality of life observed six months following surgery was maintained at two years. All types of pain symptoms improved; pre-menstrual pain, menstrual pain, non-cyclical pain, back pain, pain with sexual intercourse, voiding and on opening the bowels. A significant reduction in the need for analgesia supported the findings of an overall reduction in pain

symptoms. Bowel symptoms including frequency, urgency, incomplete emptying and constipation also improved. This type of surgery requires enhanced laparoscopic skills, primarily because of the need to overcome distorted anatomy and operate in proximity to delicate gastrointestinal, genitourinary and vascular structures. However, clinical outcomes were good, and the rates of serious peri-operative and late complications were low, when laparoscopic excision of rectovaginal endometriosis was conducted in recognised, specialist centres.

*Strengths and weaknesses of the study*

Our study has many strengths which include the size of the sample with nearly 5000 cases, the largest datset by far reported to date in the world literature. These data were collected prospectively, minimising missing data and recall bias, were obtained from multiple centres enhancing transferability, and outcomes measurements were patient reported reducing interpreter bias. Efficacy outcomes were assessed in both the short term (at six months) and longer term (at two years) following surgery. In addition, the scale of these data and the method of collection have enabled a robust assessment of the risk of complications from this type of surgery. Precise estimates of efficacy of surgery and associated complication rates to inform clinical decision making have been lacking because relevant data available in the literature have been derived from small, single centre case series [9,10,,20,21] and in many such publications the severity of endometriotic disease has been heterogeneous or not defined.[9,10,20,21] We are aware of no other data set that has examined the laparoscopic management of rectovaginal endometriosis when it is applied across a country according to accepted best practice and within nationally approved guidance [6]. Although there may be some units in the UK that do not submit data to the BSGE national database, this would be the exception for any NHS unit carrying out large volumes of surgery as this has become the standard for commissioning of endometriosis services by NHS England.

The main limitation of our study relates to missing data from incomplete data entry, incomplete follow-up or uncompleted follow up at closure of the study. We performed

sensitivity analyses to explore the robustness of our results to incomplete follow up. The results were stable, remaining significant in some cases even when symptomatic outcomes for those women with missing data were assumed to be the worst possible outcome. Furthermore, when we restricted analysis to the seven centres providing the most complete follow-up, the observed improvement in clinical symptoms and quality of life were reproduced. Thus, it is unlikely that the impact of missing data would substantially alter clinical inferences on the efficacy of laparoscopic surgery for severe rectovaginal endometriosis.

We did not routinely collect data regarding BMI which may impact upon the incidence of surgical complications. Moreover, we did not collect data pertaining to reproductive history and fertility. Thus, we cannot comment upon the impact of these factors on clinical outcomes Whilst the lack of these baseline data may limit the generalisability of our findings we believe that our results are likely to remain externally valid in light of the magnitude and multi-centre nature of our series. We evaluated symptoms relating to bowel function in addition to reporting pain symptoms known to be associated with endometriosis. However, condition-specific validated instruments assessing bowel symptoms in rectovaginal endometriosis are lacking. The data we provide are germane to the symptoms our patients with endometriosis complain of and as such we believe have face validity. We did not collect pain diaries where detail regarding the dose and pattern of analgesic use could be obtained. As we collected a large amount of data pertaining to pain, urinary and bowel function and the impact of symptoms of quality of life, we adopted a pragmatic approach, limiting our enquiry to what type of analgesia was being used at the time of follow up. In this way we hoped to minimise the burden on the individual patient to respond enhancing completeness of data entry and follow up. A final limitations relates to our use of historical control data from the same patients prior to surgical intervention whereas the study would have benefited from a non-surgically treated control group. However, persuading a group of women with severe, refractory symptoms to continue with non-surgical treatment would be challenging.

Despite the complexity of the surgery, the overall reported perioperative and post-operative serious complication rates were relatively low at 4.7% and 2.5% respectively. Conversion to laparotomy occurred in less than 1% of cases demonstrating advances in acquisition of laparoscopic surgical skills, training and equipment. Excision of endometriosis in the posterior pelvis is a difficult surgical procedure but the improved vision and precision that laparoscopy provides may improve completeness of excision and, in skilled hands, minimise the risk of complications. The ureteric injury rate of 0.5% was similar to those reported in smaller series from single centres and that associated with hysterectomy.[22] Bowel trauma, namely unintended bowel injuries, leaking from bowel surgery and recto-vaginal fistula formation occurred in 1.2% of cases. In the context of the morbidity associated with rectovaginal endometriosis, its resistance to conventional medical treatments and the nature, complexity and efficacy of surgery, this rate of complications appears to be acceptable. Moreover, the rates of adverse events are comparable to other series from expert, single centres.[20-22] The reported incidence of complications cannot however, be used as indicative risk for patients who have care given in non-specialist endometriosis centres.

*Strengths and weaknesses in relation to other studies, discussing important differences in results*

The findings from the current study which is the largest, multicentre series by far to be reported to date, are in keeping with those published from smaller, single centre observational cohorts of women undergoing laparoscopic excision of deep endometriosis. Significant reductions in the intensity of chronic pelvic pain, dysmenorrhoea, dyspareunia and dyschezia were reported from series in the UK (57 and 137 women)[11,21], Finland (22 women)[20]. The majority of studies included in a recent extensive literature review of surgical treatment of deep endometriosis with colorectal involvement also reported improvements in pain and digestive symptoms as well as health related quality of life, although few studies

reported this latter outcome.[10] The size of the 49 included studies ranged from four to 283 cases and the total number of operations evaluated were 1791 of which 679 (38%) were rectal shaving procedures, 375 (21%) disc resections and 737 (41%) segmental resections. However, comparisons between studies were not possible because of inadequate reporting (many included studies reported 'overall improvement'), as well as inconsistent assessment, of clinical outcomes (e.g. use of interviews, bespoke questionnaires, visual analogue scales). A systematic review of 34 articles describing 1889 segmental bowel resections also showed that the vast majority of women had significant improvement in chronic pelvic pain, dysmenorrhea, dyspareunia and dyschezia at one year [9].

Safety, in addition to efficacy is necessary to justify undertaking complex laparoscopic procedures for a benign pathology albeit a condition associated with substantial morbidity. Haemorrhage greater than one litre was the most common peri-operative complication occurring in 0.9% of cases. This rate is consistent with the available literature where haemorrhage requiring blood transfusion in complicated procedures (0.3%-3.1%) depending upon the type of bowel surgery.[10] Similarly our peri-operative and post-operative complication rates were comparable to the mean (range) of complications reported within a recent review of 49 case series[10]: rectovaginal fistulae 0.3% vs. 2.7% (0%-11%); enterostomy 0.5% vs. 1.2% (0.0% - 7.0%) and pelvic abscess 0.4% vs. 0.3% (0.0% - 4.0%). Complication data from a systematic review restricted to segmental bowel resection reported a 6.4% rate of severe bowel complications (leakage 1.9%; fistula 1.8%; severe obstruction 2.7%), 2.5% rate of haemorrhage and 1% severe infection rate.[9] Our ureteric injury rate of 0.5% is in keeping with the 1% reported in another series[21] as is the low observed prevalence of unintended bowel injury, major vascular injury and urinary tract fistula. [20-22]

*Meaning of the study: possible explanations and implications for clinicians and policymakers*

This study demonstrates that women having laparoscopic excisional surgery for rectovaginal endometriosis obtain significant symptomic relief, reduction in analgesia use and improvement in their quality of life. These improvements are present at six months and

sustained at two years, with the exception of voiding difficulty. The lack of improvement in this symptom may be explained by the fact that the presence of bladder endometriosis was not an inclusion criterion for this study and so voiding complaints may be an independent symptom. This study cannot predict outcomes more than two years post-operatively but it is very encouraging that the worsening of symptom scores, analgesia use and quality of life scores post-operatively (from six months to two years) is extremely small compared to the large clinical improvement seen initially.

Rectovaginal endometriosis sits between the vagina and the rectum and thus the most consistent symptom differentiating it from the pain associated with less severe and other forms of endometriosis or adenomyosis, is pain on intercourse or 'dyspareunia'. In addition, in the more severe groups, pain on defaecation is a common symptom due to the proximity to, or invasion of, the bowel. Thus it is reassuring that the surgery resulted in a significant improvement in these symptoms and that the effect lasted for the two years of follow up. One of the side effects of all surgery is scarring and it is possible that a rectovaginal nodule of endometriosis excised may be replaced by scar tissue leading to a resumption of dyspareunia. These data would suggest that this was not the case. In addition the long term effects of surgery would suggest a lack of significant recurrence during the time scale of the study.

Laparoscopic surgical excision of rectovaginal endometriosis appears to be effective in treating chronic pelvic pain, bowel and urinary symptoms and improving health related quality of life and has an acceptable major complication rate when performed in specialist surgical centres. Women with severe and refractory symptoms adversely impacting on their quality of life should be offered laparoscopic surgical treatment in recognised endometriosis centres, where clinical outcomes are objectively audited. Commissioners of health services should restrict these highly complex surgical treatments to specialist centres to ensure an adequate case-load and where expertise is demonstrated through provision of auditable clinical outcomes.

*Unanswered questions and future research*

Future studies should collect relevant baseline clinical data including comprehensive population characteristics, indications for surgery and fertility desires. Serial, standardised short and long term follow up will enhance comparability of data and a better evaluation of the longer term effects of laparoscopic interventions for deep rectovaginal disease on symptoms. Relevant and valid outcomes should be chosen with the help of patient involvement and should include valid collection of health related quality of life data. Such studies should be controlled, where possible and ideally randomised to reduce selection bias. A randomised controlled trial (RCT) comparing excisional surgery and diagnostic laparoscopy with the same number of ports is difficult ethically because women in the placebo arm would have been referred for specialist treatment and thus would be undergoing an unnecessary surgical intervention. Future studies should consider randomising between laparoscopic surgery and non-surgical therapy or alternatively compare different laparoscopic surgical interventions. The morbidity associated with rectovaginal endometriosis has a substantial economic impact due to the related reduction in activity both socially and in the work place. Thus, any future studies should include formal economic analysis to weigh the costs of surgical management against clinical, health service and societal gains.

**Conclusions**

This study presents by far the largest, multi-centre rectovaginal endometriosis surgical series in the literature both in relation to clinical outcomes and complication rates . Deep endometriosis is associated with a high disease burden and limited access to effective medical and surgical treatment is a large unmet need. Indeed, half our study population had undergone previous surgery for endometriosis mostly in non-specialist centres. Women suffer with chronic pain and psychological symptoms which impairs their quality of life.

Health services and the wider economy suffer through utilisation of substantial health care resources and restrictions placed upon women's physical functioning which can lead to absenteeism and the inability to fulfil domestic and professional duties.[23] The impact of endometriosis on quality of life is well recognised [21,24–26] and well demonstrated in the current study where the median pre-operative EQ global VAS score was only 55/100 and the median pre-operative EQ5D index score only 0.525. It is also widely acknowledged that surgical management of deep endometriosis involving the rectovaginal septum and/or bowel is technically challenging and can be associated with high rates of serious complications. However, women with deep endometriosis often have severe and refractory symptoms adversely impacting on their quality of life[6–8] justifying the need for effective surgical treatment even if associated with potentially serious complications.

Our large, multicentre dataset demonstrates significant improvements in a variety of pain and functional bowel symptoms from laparoscopic excisional surgery. The substantial and sustained improvements in pain symptoms and health related quality of life and reassuringly low rates of major perioperative and post-operative complications supports this form of surgical treatment when conducted in specialist endometriosis centres. Future studies should include formal economic analyses to weigh the costs of surgical management against clinical, health service and societal gains.

**What is already known on this subject**

- Deep rectovaginal endometriosis is common, causing serious morbidity from chronic pelvic pain, subfertility, sexual dysfunction, bowel and urinary dysfunction as well as utilising health care and wider societal resources.

- Laparoscopic surgical excision is increasingly used to treat severe rectovaginal endometriosis in the absence of safe and effective medical therapy, but it requires advanced surgical skills due to its complexity and potential for serious complications.

- There is no consensus on the effectiveness and risks of laparoscopic surgical excision of rectovaginal endometriosis because evidence from large, multi-centre series with clearly defined populations are lacking.

**What this paper adds**

- Laparoscopic surgical excision of rectovaginal endometriosis appears to be effective in treating chronic pelvic pain, sexual dysfunction, bowel and urinary symptoms and improving health related quality of life and has a low major complication rate when performed in specialist surgical centres.

- Women with severe and refractory symptoms adversely impacting on their quality of life should be offered laparoscopic surgical treatment in recognised endometriosis centres where clinical outcomes are audited.

- Future studies should randomise between laparoscopic surgery and non-surgical therapy incorporating health economic analyses and compare different laparoscopic surgical interventions for treating rectovaginal endometriosis.

**Copyright statement**



**Competing interests:**

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: support from the British Society for Gynaecological Endoscopy (BSGE) for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. All authors with the exception of TC are members of the BSGE.

**Contributorship statement**

The contributorship of the authors is as follows: Mr Dominic Byrne maintained and upgraded the endometriosis database, designed the study and analysis, provided data, contributed to data interpretation and drafting of the manuscript. Dr Tamara Curnow - conducted the statistical analysis, data interpretation and contributed to drafting of the manuscript. Mr Paul Smith

designed the study, conducted literature and reference review and contributed to drafting of the manuscript. Mr Ertan Saridogan – provided data, contributed to data interpretation and drafting of the manuscript. Mr Alfred Cutner – Responsible for set up of the BSGE endometriosis centres project, provided data, contributed to data interpretation and drafting of the manuscript. Professor T. Justin Clark – chaired the BSGE Endometriosis Centres Scientific Advisory Group, designed the study, contributed to data interpretation and drafting of the manuscript and is the Guarantor on behalf of the BSGE Endometriosis centres research group

**Ethics:**

All patients gave written consent to have their data stored on the BSGE database and for its subsequent use in scientific research and publication. Written consent was obtained each time symptoms and quality of life data were collected. The database is managed in accordance with the data protection act, data are encrypted and the database is hosted by a third party that is paid by the BSGE for this service. The BSGE designed and developed the database. The BSGE is a charity which raises funds from its membership and scientific meeting sponsorship. All hopsitals where clinicians enter data are informed in writing by the BSGE to the CEO and Medical Director about the patient data storage on the BSGE endometriosis database to ensure their agreement. Two authors were funded to carry out initial research (PS) and to perform statistical analysis on the data (TC).

**STROBE checklist:**

The checklist has been attached and uploaded as a supplemental file to the submitted paper. We have paid particular attention to items which ask authors to "explain the scientific

background and rationale for the investigation being reported" and "state specific objectives, including any prespecified hypotheses."

**Study funding:**

The BSGE is a registered charity and paid for the development and maintenance of the Endometriosis database. The BSGE provided limited funding for one author to perform background research and literature review (PS) and one author (TC) to undertake statistical analysis

**Study sponsor / funder role:**

Each hospital that contributed data acted as a study sponsor in that they agreed to collection of data from their respective endometriosis centre and it being stored on the BSGE endometriosis database for research.

**Statement of the independence of researchers from funders:**

There was no direct research funding apart from the BSGE financial support to set up and administer the database, employ a statistician and a research fellow

**Authors statement:**

We confirm that all authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

**Transparency declaration:**

I, T Justin Clark, on behalf of all other named authors affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

**Data sharing statement:**

The full dataset is available from the corresponding author at t.j.clark@doctors.org.uk

**Study registration number and name of register for any study type:**

Not registered. The BSGE website describes the endometriosis centres project and the establishment of the endometriosis patient registry (endometriosis database) which meets the standards set by NICE for such records.

**Aknowledgements**

We are grateful to Jeremy Wright and Adam Moors who designed and established the BSGE endometriosis database and Dominic Byrne who upgraded it to increase completeness of data collection and follow up.

We are grateful to the BSGE Scientific Advisory Group who approve research on BSGE endometriosis database data and have scrutinised the manuscript. The members are: Prof Justin Clark (chair), Dominic Byrne, Oliver Chappatte, Alfred Cutner, Chris Guyer, Ertan Saridogan and Robert Richardson.

We would like to thank and acknowledge all the BSGE Endocentre teams for contributing to this work by entering their data on the BSGE Endometriosis database, they are listed alphabetically below with number of cases in brackets and name of lead Gynaecologist. The seven centres referred to in the paper with best follow up are marked in bold.

Aberdeen (99) Lucky Saraswat, **ACEMIG (140) Shaheen Khazali**, Altnergavin (36) Iris Menninger, Birmingham (58) Yousri Afifi, Castle Hill (103) Kevin Phillips, CEMIG (199) Saikat Banerjee, Chelsea and Westminster (258) Robert Richardson, Chester (88) Jeremy Hawe, Colchester (81) Barry Whitlow, **Cornwall (257) Dominic Byrne**, Croydon University hospital (57) Emmanuel Ofuasia Dewsbury/Elland (121) Ashwini Trehan, Dorset (57) Tyrone Carpenter, Endometriosis CaRe Oxford (164) Christian Becker, Exeter (23) James Clark, Exppect Edinburgh (52) Stuart Jack, **Guy's and Thomas' (29) Kumar Kunde** Gynaecology.co (98) Alfred Cutner, Homerton (21) Chris Barnick, Imperial (75) Alan Farthing, James Cook Hospital (111) Graham Phillips, Kings College (132) John Bidmead, Lancashire women's and newborn (31) Mohamed Abdel-Aty, Liverpool women's (85) George Botros, Luton and Dunstable (35) Marlin Mubarak, , Mid Yorks (46) Christian Kremer, Norfolk and Norwich University Hospital (53) Edward Morris, North Middlesex (34) Stanley Okolo, **North west pelvic pain, Manchester (87) Edmond Edi-Osagi**, Northwick Park Hospital (81) Kamel Shehata-Iskander, Penine (63) Gaity Ahmad, Plymouth (53) Jonathan Frappell, **Preston Royal, Lancashire (31)**

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**Table 1.** Patient reported symptoms prior to laparoscopic surgical excision of rectovaginal endometriosis and at six months, one year and two years post treatment (median scores are presented (0-10 for the first nine symptoms and 0-4 for the remaining 5 symptoms) with total number of responses in round brackets and 95% confidence interval of the median in square brackets). A lower score is associated with less severe symptoms.

| Pre menstrual pain | Pre-surgery | 6 months | 12 months | 24 months | Short – term[1] (baseline vs. 6 months) | Long – term[1] (baseline vs. 24 months) | Change[2] (6 months vs. 24 months) |
|---|---|---|---|---|---|---|---|
| Premenstrual pain* | 7 [7 7] (3853) | 3 [3 3] (1817) | 3 [3 4] (1120) | 3 [3 4] (531) | 0.000v (1785) | 0.000v (527) | 0.000^ (358) |
| Menstrual pain* | 9 [9 9] (3857) | 5 [4 5] (1810) | 5 [4 5] (1116) | 5 [4 6] (524) | 0.000v (1781) | 0.000v (522) | 0.004^ (354) |
| Noncyclical pelvic pain | 6 [6 6] (4155) | 2 [2 2] (2170) | 2 [2 2] (1360) | 3 [2 3] (658) | 0.000v (2160) | 0.000v (656) | 0.000^ (453) |
| Deep dyspareunia | 6 [5 6] (3987) | 1 [0 1] (1998) | 1 [1 1] (1247) | 2 [1 2] (608) | 0.000v (1952) | 0.000v (598) | 0.000^ (403) |
| Cyclical dyschezia* | 6 [6 6] (3852) | 1 [0 1] (1834) | 1 [0 1] (1157) | 2 [1 3] (536) | 0.000v (1799) | 0.000v (535) | 0.000^ (359) |
| Non cyclical dyschezia | 3 [2 3] (4136) | 0 [0 0] (2178) | 0 [0 0] (1374) | 0 [0 1] (655) | 0.000v (2162) | 0.000v (646) | 0.000^ (449) |
| Lower back pain | 6 [6 6] (4151) | 3 [3 3] (2188) | 3 [3 3] (1376) | 3 [3 4] (660) | 0.000v (2172) | 0.000v (656) | 0.027^ (457) |
| Bladder pain or pain passing urine | 0 [0 0] (4085) | 0 [0 0] (2162) | 0 [0 0] (1369) | 0 [0 0] (652) | 0.000v (2122) | 0.000v (638) | 0.034^ (446) |
| Difficulty emptying bladder | 0 [0 0] (4003) | 0 [0 0] (2135) | 0 [0 0] (1360) | 0 [0 0] (650) | 0.000v (2075) | 0.105 (628) | 0.002^ (440) |
| Frequent bowel movements | 2 [2 2] (3996) | 2 [2 2] (2154) | 2 [2 2] (1372) | 2 [2 2] (660) | 0.000v (2087) | 0.012v (626) | 0.051 (451) |
| Urgent bowel movements | 1 [1 1] (3997) | 1 [1 1] (2154) | 1 [1 1] (1371) | 1 [1 1] (658) | 0.000v (2091) | 0.006v (623) | 0.000^ (449) |
| Incomplete emptying sensation | 1 [1 1] (3981) | 1 [1 1] (2149) | 1 [1 1] (1372) | 1 [1 1] (659) | 0.000v (2075) | 0.000v (623) | 0.004^ (447) |
| Constipation | 2 [1 2] (4001) | 1 [1 1] (2156) | 1 [1 1] (1368) | 1 [1 1] (658) | 0.000v (2091) | 0.002v (628) | 0.001^ (449) |
| Blood in the stool | 0 [0 0] (3894) | 0 [0 0] (1912) | 0 [0 0] (1206) | 0 [0 0] (546) | 0.000v (1831) | 0.038v (507) | 0.001^ (350) |

[1] Statistical comparison (Mann Whitney U test) of short term symptom scores (6 months post surgery) and long term symptom scores (2 years post surgery) with baseline scores (pre-surgery)
[2] Statistical comparison (Mann Whitney U test) of change in symptom scores over time post treatment (between 6 months and 2 years)
^ = statistically significant increase, v = statistically significant decrease.
Note that there is some variation in total number of responses depending on whether patients chose not to answer some questions
* Excludes patients that had a hysterectomy prior to this surgery.

**Table 2.** Median scores for patient reported quality of life prior to treatment and at six months, one year and two years post treatment with total number of patients in round brackets and 95% confidence intervals in square brackets. Median EQVAS lies in the range 0-100 with a higher score associated with a better quality of life. The other median scores (EQ5D) lie in the range 0-2 where a lower score is associated with a better quality of life.

| **Pre menstrual pain** | **Pre-surgery** | **6 months** | **12 months** | **24 months** | **Short – term[2] (baseline vs. 6 months)** | **Long – term[2] (baseline vs. 24 months)** | **Change[3] (6 months vs. 24 months)** |
|---|---|---|---|---|---|---|---|
| EQVAS numeric[1] | 55 [55 57] (4015) | 80 [75 80] (2050) | 80 [75 80] (1247) | 76 [75 80] (575) | 0.000^ (2045) | 0.000^ (573) | 0.024v (396) |
| EQ5D Usual Activities | 1 [1 1] (4005) | 0 [0 0] (2051) | 0 [0 0] (1250) | 0 [0 0] (574) | 0.000v (2042) | 0.000v (570) | 0.477 (395) |
| EQ5D Pain discomfort | 1 [1 1] (4004) | 1 [1 1] (2050) | 1 [1 1] (1252) | 1 [1 1] (573) | 0.000v (2041) | 0.000v (569) | 0.427 (394) |
| EQ5D Anxiety depression | 1 [1 1] (3991) | 0 [0 0] (2049) | 0 [0 0] (1252) | 0 [0 0] (573) | 0.000v (2033) | 0.000v (569) | 0.331 (395) |
| EQ5D Mobility | 0 [0 0] (3999) | 0 [0 0] (2046) | 0 [0 0] (1250) | 0 [0 0] (569) | 0.000v (2035) | 0.000v (563) | 0.339 (392) |
| EQ5D SelfCare | 0 [0 0] (3994) | 0 [0 0] (2033) | 0 [0 0] (1248) | 0 [0 0] (558) | 0.000v (2020) | 0.001v (548) | 0.364 (384) |
| EQ5D index[1]* | 0.689 [0.689 0.689] (3966) | 0.796 [0.796 0.796] (2032) | 0.796 [0.796 0.796] (1245) | 0.796 [0.796 0.796] (556) | 0.000^ (2010) | 0.000^ (546) | 0.043v (383) |

[1]A high Euroqol Visual Analogue Scale (EQ-VAS) score or a high EQ5D index score is associated with an improvement in QoL whereas with all other QoL and symptom scores a low value is associated with improvement.
[2] Statistical comparison (Mann Whitney U test ) of short term symptom scores (6 months post surgery) and long term symptom scores (2 years post surgery) with baseline scores (pre-surgery)
[3] Statistical comparison (Mann Whitney U test ) of change in symptom scores over time post treatment (between 6 months and 2 years)
^ = statistically significant increase, v = statistically significant decrease
Note that there is some variation in total number of responses depending on whether patients chose not to answer some questions.
* EQ5D index of 1 is equivalent to perfect health and 0 equivalent to death. Means are reported rather than medians..

**Table 3.** Analgesia use prior to surgery and at six months, one year and two years post surgery. Percentage of patients using medication with total number of patients in brackets.

| Pre menstrual pain | Pre-surgery | 6 months | 12 months | 24 months | Short – term[1] (baseline vs. 6 months) | Long – term[1] (baseline vs. 24 months) | Change[2] (6 months vs. 24 months) |
|---|---|---|---|---|---|---|---|
| Paracetamol | 76.0% (4118) | 59.8%(1934) | 60.6% (1235) | 61.4% (610) | 0.000v (1915) | 0.000v (604) | 0.001^ (388) |
| NSAID | 69.8% (4099) | 48.9%(1924) | 48.3% (1229) | 52.0% (603) | 0.000v (1903) | 0.000v (593) | 0.013^ (385) |
| Opiates | 28.1% (3953) | 16.1% (1895) | 16.8% (1214) | 16.6% (592) | 0.000v (1859) | 0.000v (575) | 0.006^ (376) |

NSAID – non-steroidal anti-inflammatory drug

[1] Statistical comparisons of short term change in analgesia use(6 months post surgery) and long term change in analgesia use (2 years post surgery) with baseline analgesia use (pre-surgery) assessed using a 2-tailed sign test.
[2] Statistical comparison of change in analgesia use over time post treatment (between 6 months and 2 years) using a 2-tailed sign-test.
^ = statistically significant increase, v = statistically significant decrease.
Note that there is some variation in total number of responses depending on whether patients chose not to answer some questions

**Table 4.** Sensitivity analysis for missing post-operative data.

| | **Short-term (6 months)[1]** | **Long–term (2 years)[1]** | **Range** |
|---|---|---|---|
| *Symptoms* | | | |
| Premenstrual pain | 9 | 8 | [0, 10] |
| Menstrual pain | 10 | 10 | [0, 10] |
| Non cyclical pelvic pain | 7 | 6 | [0, 10] |
| Deep dyspareunia | 8 | 6 | [0, 10] |
| Cyclical dyschezia | 7 | 7 | [0, 10] |
| Non cyclical dyschezia | 5 | 3 | [0, 10] |
| Low back pain | 7 | 7 | [0, 10] |
| Bladder pain | 2 | 1 | [0, 10] |
| Voiding difficulty | 0 | NS | [0, 10] |
| Frequent bowel movements[2] | 3 | 3 | [0, 4] |
| Urgent bowel movements[2] | 2 | 2 | [0, 4] |
| Incomplete bowel movements[2] | 2 | 2 | [0, 4] |
| Constipation[2] | 2 | 2 | [0, 4] |
| Blood in the stool[2] | 0 | 1 | [0, 4] |
| | | | |
| *Quality of life*[2] | | | |
| EQ Visual analogue score | 40 | 55 | [0, 100] |
| EQ5D Usual Activities | 2 | 1 | [0, 2] |
| EQ5D Pain and discomfort | 2 | 2 | [0, 2] |
| EQ5D Anxiety and depression | 1 | 1 | [0, 2] |
| EQ5D Mobility | 1 | 1 | [0, 2] |
| EQ5D Self care | 1 | 1 | [0, 2] |
| EQ5D index | 0.45 | 0.65 | [-0.594, 1] |

[1] The worst possible score that could be reported for all the missing post-operative data in order for the short-term (six months) or long-term statistics in Tables 3 & 4 to still be significant (The test statistics that were not significant (NS) to start with have not been included).

[2] A high EuroQol Visual Analogue Scale (EQ-VAS) or EQ5D index score is associated with an improvement in QoL whereas with all other QoL and symptom scores a low value is associated with improvement.

**Table 5.** Sensitivity analysis for missing post-operative data restricted to the seven British Society for Gynaecological Endoscopy (BSGE) Endometriosis Centres with the most complete follow-up.

| | **Short-term (6 months)[1]** | **Long–term (2 years)[1]** | **Range** |
|---|---|---|---|
| *Symptoms* | | | |
| Premenstrual pain | 10 | 7 | [0, 10] |
| Menstrual pain | 10 | 9 | [0, 10] |
| Non cyclical pelvic pain | 10 | 5 | [0, 10] |
| Deep dyspareunia | 10 | 5 | [0, 10] |
| Cyclical dyschezia | 10 | 5 | [0, 10] |
| Non cyclical dyschezia | 7 | 4 | [0, 10] |
| Low back pain | 10 | 5 | [0, 10] |
| Bladder pain | 4 | 1 | [0, 10] |
| Voiding difficulty | 1 | NS | [0, 10] |
| Frequent bowel movements[2] | 2 | NS | [0, 4] |
| Urgent bowel movements[2] | 3 | NS | [0, 4] |
| Incomplete bowel movements[2] | 2 | NS | [0, 4] |
| Constipation[2] | 2 | NS | [0, 4] |
| Blood in the stool[2] | 2 | 1 | [0, 4] |
| | | | |
| *Quality of life*[2] | | | |
| EQ Visual analogue score | 0 | 55 | [0, 100] |
| EQ5D Usual Activities | 1 | 1 | [0, 2] |
| EQ5D Pain and discomfort | 2 | 2 | [0, 2] |
| EQ5D Anxiety and depression | 2 | 1 | [0, 2] |
| EQ5D Mobility | 0 | 1 | [0, 2] |
| EQ5D Self care | 1 | NS | [0, 2] |
| EQ5D index | -0.594 | 0.65 | [-0.594, 1] |

[1] The worst possible score that could be reported for all the missing post-operative data in order for the short-term (six months) or long-term statistics in Tables 3 & 4 to still be significant (The test statistics that were not significant (NS) to start with have not been included).

[2] A high EuroQol Visual Analogue Scale (EQ-VAS) or EQ5D index score is associated with an improvement in QoL whereas with all other QoL and symptom scores a low value is associated with improvement.

**Table 6**. Incidence of peri-operative and post-operative complications.

| Peri-operative complication | Number of patients | Incidence |
|---|---|---|
| | | |
| Haemorrhage >1litre | 43 | 0.9% |
| Ureteric injury | 24 | 0.5% |
| Unexpected bowel injury | 28 | 0.6% |
| Unexpected bladder injury | 17 | 0.4% |
| Unexpected vascular injury | 10 | 0.2% |
| Epigastric injury | 4 | 0.1% |
| Conversion to laparotomy | 41 | 0.9% |
| Colostomy | 9 | 0.2% |
| Ileostomy | 14 | 0.3% |
| Unplanned Removal of any other organ | 11 | 0.2% |
| Death | 0 | 0.0% |
| **Total suffering any perioperative complication** | **220** | **4.7%** |
| | | |
| **Post-operative complication** | | |
| | | |
| Pelvic haematoma | 37 | 0.8% |
| Pelvic Abscess | 17 | 0.4% |
| Urinary tract leak | 11 | 0.2% |
| Bowel leak | 17 | 0.4% |
| Urinary tract fistula | 2 | 0.0% |
| Bowel fistula | 12 | 0.3% |
| Severe sepsis | 10 | 0.2% |
| Pulmonary embolism | 1 | 0.0% |
| **Total suffering any post operative complication** | **120** | **2.5%** |
| | | |

Note that some patients suffered more than one complication

**Table 7.** Incidence of bowel complication related to the type of surgery performed on the bowel.

| Type of bowel surgery | Number of operations | UBI | Leak | Fistula | Total |
|---|---|---|---|---|---|
| No Bowel Surgery | 1740 | 6 (0.3%) | 3 (0.2%) | 2 (0.1%) | 11 (0.6%) |
| Shaved | 2746 | 18 (0.7%) | 6 (0.2%) | 5 (0.2%) | 29 (1.1%) |
| Disc Resection | 54 | 0 (0.0%) | 4 (7.4%) | 3 (5.6%) | 5 (9.3%) |
| Segmental Resection | 181 | 4 (2.2%) | 4 (2.2%) | 2 (1.1%) | 7 (3.9%) |
| Total | 4721 | 28 (0.6%) | 17 (0.4%) | 12 (0.3%) | 52 (1.1%) |

*UBI = unexpected bowel injury at the time of surgery. Leak = any bowel leak identified after primary surgery. Fistula formation is a late complication from surgery.*

**Supplementary table 1.** Patient reported symptoms prior to laparoscopic surgical excision of rectovaginal endometriosis and at six months, one year and two years post treatment (median scores are presented (0-10 for the first nine symptoms and 0-4 for the remaining 5 symptoms) with total number of patients in round brackets and 95% confidence interval of the median in square brackets). Analysis restricted to the seven British Society for Gynaecological Endoscopy (BSGE) Endometriosis Centres with the most complete follow-up. A lower score is associated with less severe symptoms.

| | Pre-surgery | 6 months | 12 months | 24 months | Short – term[1] (baseline vs. 6 months) | Long – term[1] (baseline vs. 24 months) | Change[2] (6 months vs. 24 months) |
|---|---|---|---|---|---|---|---|
| Premenstrual pain* | 7 [6 7] (632) | 3 [2 3] (436) | 3 [2 3] (278) | 4 [3 5] (119) | 0.000v (427) | 0.000v (119) | 0.108 (97) |
| Menstrual pain* | 9 [8 9] (633) | 4 [3 5] (435) | 4 [4 5] (278) | 6 [5 7] (118) | 0.000v (427) | 0.000v (118) | 0.017^ (96) |
| Noncyclical pelvic pain | 6 [5 6] (676) | 2 [2 2] (517) | 2 [2 3] (333) | 3 [2 4] (152) | 0.000v (516) | 0.000v (151) | 0.007^ (125) |
| Deep dyspareunia | 6 [5 6] (646) | 1 [0 2] (453) | 1 [0 2] (303) | 2 [1 3] (137) | 0.000v (449) | 0.000v (136) | 0.317 (105) |
| Cyclical dyschezia* | 6 [5 6] (632) | 0 [0 0] (444) | 1 [0 2] (289) | 3 [1 4] (125) | 0.000v (434) | 0.000v (125) | 0.000^ (100) |
| Non cyclical dyschezia | 3 [2 3] (673) | 0 [0 0] (519) | 0 [0 0] (339) | 0 [0 2] (151) | 0.000v (516) | 0.000v (149) | 0.192 (123) |
| Lower back pain | 6 [5 6] (671) | 2 [2 3] (521) | 2 [2 3] (341) | 4 [2 5] (152) | 0.000v (515) | 0.000v (151) | 0.905 (126) |
| Bladder pain or pain passing urine | 0 [0 1] (668) | 0 [0 0] (518) | 0 [0 0] (337) | 0 [0 0] (153) | 0.000v (511) | 0.000v (151) | 0.560 (126) |
| Difficulty emptying bladder | 0 [0 0] (662) | 0 [0 0] (516) | 0 [0 0] (336) | 0 [0 0] (153) | 0.000v (506) | 0.136 (150) | 0.558 (124) |
| Frequent bowel movements | 2 [2 2] (665) | 2 [2 2] (521) | 2 [2 2] (340) | 2 [2 3] (151) | 0.000v (513) | 0.343 (146) | 0.096 (125) |
| Urgent bowel movements | 1 [1 1] (665) | 1 [1 1] (521) | 1 [0 1] (339) | 1 [1 2] (150) | 0.000v (513) | 0.524 (145) | 0.000^ (124) |
| Incomplete emptying sensation | 1 [1 2] (662) | 1 [1 1] (519) | 1 [0 1] (340) | 1 [1 2] (153) | 0.000v (509) | 0.426 (147) | 0.001^ (126) |
| Constipation | 1 [1 2] (664) | 1 [1 1] (521) | 1 [1 1] (340) | 1 [1 1] (151) | 0.000v (512) | 0.093 (146) | 0.024^ (125) |
| Blood in the stool | 0 [0 0] (641) | 0 [0 0] (450) | 0 [0 0] (294) | 0 [0 0] (125) | 0.000v (439) | 0.019v (118) | 0.074 (98) |

[1] Statistical comparison (Mann Whitney U test) of short term symptom scores (6 months post surgery) and long term symptom scores (2 years post surgery) with baseline scores (pre-surgery)
[2] Statistical comparison (Mann Whitney U test) of change in symptom scores over time post treatment (between 6 months and 2 years)
^ = statistically significant increase, v = statistically significant decrease.
Note that there is some variation in total number of responses depending on whether patients chose not to answer some questions
* Excludes patients that had a hysterectomy prior to this surgery.

**Supplementary table 2.** Median scores for patient reported quality of life prior to treatment and at six months, one year and two years post treatment with total number of patients in round brackets and 95% confidence intervals in square brackets restricted to the seven British Society for Gynaecological Endoscopy (BSGE) Endometriosis Centres with the most complete follow-up. Median EQVAS lies in the range 0-100 with a higher score associated with a better quality of life. Mean EQ5D index is 1 for perfect health and 0 for death with possible negative values associated with 'worse than death'. The other median scores (EQ5D) lie in the range 0-2 where a lower score is associated with a better quality of life.

| | **Pre-surgery** | **6 months** | **12 months** | **24 months** | **Short – term[2]** **(baseline vs. 6 months)** | **Long – term[2]** **(baseline vs. 24 months)** | **Change[3]** **(6 months vs. 24 months)** |
|---|---|---|---|---|---|---|---|
| EQVAS numeric[1] | 55 [50 60] (664) | 80 [80 80] (510) | 80 [75 80] (328) | 75 [70 80] (136) | 0.000^ (508) | 0.000^ (136) | 0.036v (116) |
| EQ5D Usual Activities | 1 [1 1] (666) | 0 [0 0] (510) | 0 [0 0] (330) | 0 [0 1] (135) | 0.000v (510) | 0.000v (135) | 0.140 (116) |
| EQ5D Pain discomfort | 1 [1 1] (667) | 1 [0 1] (510) | 1 [0 1] (332) | 1 [1 1] (135) | 0.000v (510) | 0.000v (135) | 0.025^ (116) |
| EQ5D Anxiety depression | 1 [1 1] (663) | 0 [0 0] (510) | 0 [0 0] (332) | 0 [0 0] (134) | 0.000v (507) | 0.000v (134) | 0.490 (116) |
| EQ5D Mobility | 0 [0 0] (667) | 0 [0 0] (510) | 0 [0 0] (332) | 0 [0 0] (134) | 0.000v (510) | 0.000v (134) | 0.034^ (116) |
| EQ5D SelfCare | 0 [0 0] (666) | 0 [0 0] (509) | 0 [0 0] (332) | 0 [0 0] (135) | 0.000v (508) | 0.134 (135) | 0.453 (116) |
| EQ5D index[1]* | 0.673 [0.620 0.689] (662) | 0.796 [0.796 0.812] (509) | 0.796 [0.796 0.848] (330) | 0.796 [0.743 0.796] (134) | 0.000^ (506) | 0.000^ (134) | 0.008v (116) |

[1]A high Euroqol Visual Analogue Scale (EQ-VAS) score or a high EQ5D index score is associated with an improvement in QoL whereas with all other QoL and symptom scores a low value is associated with improvement.
[2] Statistical comparison (Mann Whitney U test ) of short term symptom scores (6 months post surgery) and long term symptom scores (2 years post surgery) with baseline scores (pre-surgery)
[3] Statistical comparison (Mann Whitney U test ) of change in symptom scores over time post treatment (between 6 months and 2 years)
^ = statistically significant increase, v = statistically significant decrease.
Note that there is some variation in total number of responses depending on whether patients chose not to answer some questions.
* EQ5D index of 1 is equivalent to perfect health and 0 equivalent to death. Means are reported rather than medians..

**Supplementary table 3.** Analgesia use prior to surgery and at six months, one year and two years post surgery restricted to the seven British Society for Gynaecological Endoscopy (BSGE) Endometriosis Centres with the most complete follow-up. Percentage of patients using medication with total number of patients in brackets.

| | Pre-surgery | 6 months | 12 months | 24 months | Short – term[1] (baseline vs. 6 months) | Long – term[1] (baseline vs. 24 months) | Change[2] (6 months vs. 24 months) |
|---|---|---|---|---|---|---|---|
| Paracetamol | 68.3% (672) | 51.1% (464) | 50.3% (302) | 56.3% (144) | 0.000v (461) | 0.002v (142) | 0.031^ (100) |
| NSAID | 74.0% (672) | 48.0% (465) | 47.0% (302) | 59.0% (144) | 0.000v (462) | 0.053 (142) | 0.003^ (100) |
| Opiates | 27.2% (669) | 16.6% (465) | 16.9% (301) | 25.7% (144) | 0.000v (462) | 0.418 (142) | 0.001^ (100) |

Denominator (responses) shown in parentheses

NSAID – non-steroidal anti-inflammatory drug

[1] Statistical comparisons of short term change in analgesia use (6 months post surgery) and long term change in analgesia use (2 years post surgery) with baseline analgesia use (pre-surgery) assessed using a 2-tailed sign test.
[2] Statistical comparison of change in analgesia use over time post treatment (between 6 months and 2 years) using a 2-tailed sign-test.
^ = statistically significant increase, v = statistically significant decrease.
Note that there is some variation in total number of responses depending on whether patients chose not to answer some questions

STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No | Recommendation |
|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract **Page 1** |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Pages 2-3** |
| **Introduction** | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported **Pages 4-5** |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses **Page 5** |
| **Methods** | | |
| Study design | 4 | Present key elements of study design early in the paper **Page 5** |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page 5** |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Pages 5-6**<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Pages 6-8** |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Pages 6-8** |
| Bias | 9 | Describe any efforts to address potential sources of bias **Pages 8-9** |
| Study size | 10 | Explain how the study size was arrived at **Not done – largest prospective cohort in the world by far – decision to analyse and publish once large number obtained - 5000; Not a trial so no formal sample size calculation** |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Pages 6-8** |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding **Pages 8-9** |
| | | (*b*) Describe any methods used to examine subgroups and interactions **Pages 8-9** |
| | | (*c*) Explain how missing data were addressed **Pages 8-9** |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **Pages 8-9**<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of |

sampling strategy

(*e*) Describe any sensitivity analyses **Pages 8-9**

Continued on next page

| | | |
|---|---|---|
| **Results** | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Page 9** |
| | | (b) Give reasons for non-participation at each stage **Not done - LTFU presented** |
| | | (c) Consider use of a flow diagram **Not done – not an RCT or controlled study** |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Page 9-11** |
| | | (b) Indicate number of participants with missing data for each variable of interest **Each variable as number of participants** |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **Table 2-4** |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time **Table 1-4** |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Page 9-11** |
| | | (*b*) Report category boundaries when continuous variables were categorized **Not applicable** |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **Not applicable** |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **Page 12, Table 5** |
| **Discussion** | | |
| Key results | 18 | Summarise key results with reference to study objectives **Pages 13 and 20** |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Pages 13-15** |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Pages 15-16** |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results **Pages 16-17** |
| **Other information** | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Page 23** |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.