PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Laparoscopic excision of deep rectovaginal endometriosis in BSGE Endometriosis Centres: A multicentre prospective cohort study
AUTHORS	Byrne, Dominic; Curnow, Tamara; Smith, Paul; Cutner, Alfred; Saridogan, Ertan; Clark, T

VERSION 1 – REVIEW

REVIEWER	Paolo Vercellini Department of Clinical Sciences and Community Health, Università degli Studi, and Department for the Mother, Child, and Newborn Health, Fondazione Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy Disclosure of intellectual competing interest I have a different vision on rectovaginal endometriosis management with respect to that of the authors. I am in favour of long-term medical management, and believe that surgery should be reserved for symptomatic patients who do not respond, do not tolerate, or refuse progestins, for those who have contraindications to progestins or who seek a natural conception, and those who have subocclusive bowel lesions or ureteral stenosis causing hydroureteronephrosis.
REVIEW RETURNED	25-Jun-2017

GENERAL COMMENTS	Byrne and co-workers conducted a large, multicentre, prospective cohort study on more than four thousands women who underwent laparoscopic surgical excision of rectovaginal endometriosis. At 6-month follow-up pain symptoms and health-related quality of life, as measured with validated scales, greatly improved and remained stable in those women who were followed for up to 2 years. The manuscript is well written, simple and clear. The study is valuable not only for the large number of women included and the prospective design but, importantly, also because it has been conducted in many hospitals within U.K., thus substantially increasing the generalisability of the results. Indeed, generalisability of surgical outcomes is among the main problems in rectovaginal endometriosis management. The evidence provided has been obtained through well-planned and intense collaborative efforts. The organisers of this study should be commended for what will most likely become the future reference for the definition of the effect of surgery in this technically demanding clinical condition. For this very reason, the authors also take a great responsibility, as many patients with rectovaginal endometriosis will decide whether to undergo surgery or alternative treatments also based on the results here presented and the accompanying comments.

	Abundant published evidence, including RCTs, does not support the notion that surgery is the only mean to deal with rectovaginal endometriosis (see page 5, "there is limited evidence supporting the sustained effectiveness and acceptability of medical therapies in improving the symptoms of rectovaginal endometriosis"; page 16, "its resistance to conventional medical treatments"; page 21, "in the absence of safe and effective medical therapy"). Specific comments 1. The definition of rectovaginal endometriosis is unclear. Rectovaginal endometriosis implies the endometriotic infiltration of the posterior vaginal fornix and of the tunica muscularis of the anterior rectal wall. If this is not the case, then many women did not have "rectovaginal endometriosis", but instead endometriosis of the Douglas pouch, such as fibrotic placques or nodules. This has not only semantic, but also surgical implications. In fact, the surgical treatment of real rectovaginal endometriosis necessitates at least vaginal opening and resection, and sometimes low anterior rectal resection. Moreover, the preoperative diagnosis of rectovaginal endometriosis is based on the presence of bluish and reddish nodules at vaginal inspection, on positive biopsies, on vaginal/rectal US findings, and recto-sigmoidoscopy. This does not seem to have been the case here, as only an indirect indicator of deep Douglas pouch lesions has been adopted as a diagnostic criterion, that is, dissection of the para-rectal space. How could the authors be certain that rectovaginal endometriosis has been excised in all the study-patients? This is important because the incidence of major complications, including bowel leak, rectovaginal fistula formation, and ureteral lesions is strictly related with the type of lesions removed and with the extension of the surgical excision. Women must be offered a precise estimate of the incidence of major complications for this specific type of procedure, therefore, knowing exactly what was present and what was removed is relevant. In the experience of this reviewer, women take the decision regarding whether to undergo surgery for rectovaginal endometriosis equally on risk and benefit estimates. The eventuality of underestimating risks should be limited. The authors state at page 17 that the observed prevalence (incidence?) of complication was relatively low and compared well with published reports. It is difficult to judge this comment, because it is not known whether vaginal lesions were present and if the posterior fornix was opened and excised. Some details suggest that not all women had real rectovaginal endometriosis. Page 11, "a rectovaginal nodule was present in 68.6% women"; "there was endometriosis present on the rectum in 54.7% women"; no mention is made regarding vaginal resection; apparently no ureteral-neocystotomy was performed because of ureteral stenosis and this seems surprising given the exceedingly high number of patients; neurogenic bladder atony, a postoperative complication typical of radical rectovaginal endometriosis resection, does not seem to have been reported. How many patients had a portion of their vagina removed?

	2. Those patients who underwent hysterectomy and/or bilateral oophorectomy before or after the index surgical procedure should be excluded, as this introduces heterogeneity. This study should answer a specific question, i.e., which was the magnitude of the effect of laparoscopic surgery in reproductive age women with their uterus and at least on ovary present, and who underwent a conservative procedure for symptomatic deep endometriosis. This is what most women with these endometriosis forms would like to know. Previous surgery was already performed in more than half of the study population (page 10), and further confounding should be avoided. 3. Importantly, "there were no cases of malignancy in any of the endometriosis specimens" (page 11). This finding is not commented in the Discussion section, but it should, especially considering the very large number of operated women. It is important to know that in rectoveginal endometriosis forms the oncological risk is exceedingly low. When ovarian endometriomas are present, the decision to operate is often taken also based on the potential presence of malignant lesions. 4. Six-month follow-up questionnaires were available for only half of the participants. This seems a low proportion and the authors should explain in more detail the reason(s) for this. The proportion drops to about one third of the patients at 1-year follow-up, and to about one fifth at 2-year follow-up. In general, participants lost to follow-up are considered a subgroup at worse prognosis compared with those continuing the study. The authors addressed this problem by conducting a sensitivity analysis and maintain that the results remained substantially stable during the entire follow-up period even when considering the worst scenario. However, I wonder whether robust conclusions can be drawn on long-term effects of laparoscopic surgery on pain symptoms and health-related quality of life by applying a statistical model, when questionnaires on pain were available in 4,210 women at baseline and in only 729 at 2 years, and questionnaires on health-related quality of life were available in 4041 women at baseline and in only 644 at 2 years (page 11). Obtaining statistical advice may be wise here. 5. I could not find information on postoperative use of medical treatments. This seems crucial, as it as been demonstrated repeatedly that long-term medical therapies improve the outcomes and reduce not only symptom, but also lesion recurrence. Those participants who used postoperative medical treatments should be excluded from the analyses, as it would not be possible to discriminate between the effect of surgery and that of medications. 6. The authors state that "analgesia use was significantly reduced at six and 24 months post surgery compared to pre-operative levels for all three analgesic types". Analgesic use is considered an indicator of clinically important pain symptom persistence/recurrence. At 6-month follow-up about 60% of women were still using paracetamol (58.8%), about half were using NSAID (48.9%), and 16% were using opiate, with a reduction of, respectively, 16.2%, 20.9%, and 12.0%. Analgesic use slightly increased uring the follow-up period. The authors emphasise that the reduction in analgesic use from baseline figures was statistically significant ("a significant reduction in the need for analgesia supported the findings of an overall reduction in pain symptoms", page 14).

	However, given the large sample size, even a limited reduction is here statistically significant. I would rather consider that the proportion of women using analgesics during the entire follow-up period is still substantially high, and perplexities may arise on the real effect of surgery when this variable is contemplated. Moreover, this finding seems in contrast with the major reduction in pain scores observed when using the numerical rating scales. The authors should comment on these aspects in the Discussion section. 7. The authors note that "the incidence [of bowel complications] varied according to whether bowel surgery was undertaken and if so, what type of procedure" (page 14). Based on available data and personal experience, I could not agree more. Some post-operative large bowel complications require emergency re-operation, diverting loop ileostomy or colostomy, intensive care unit admission, and may be life-threatening. Therefore, when disc and segmental bowel resection are associated with, respectively, a 9.3% and 3.9% complication rates (page 14), there must be a very good reason to open the recto-sigmoid lumen deliberately. In my view, the main reason that renders a pre-planned bowel resection mandatory is the presence of sub-occlusive symptoms. In fact, whether it is worthwhile to take such risks only to improve dyschezia, is a decision that should be left to the woman once adequately informed about the incidence and the clinical impact of such complications. In this regard, the phrase "this rate of complications appears to be acceptable" (page 16) is unclear. Only the woman should judge if this rate of complications is acceptable for her, after being informed that colorectal endometriosis is a benign condition, and there is no evidence that lesions systematically progress and cause occlusion when not excised. The same is true for the sentence "justifying the need for effective surgical treatment even if associated with potentially serious complications" (page 20). Again, this should be an individual patient's judgement, not a general judgement made by surgeons. Some authors suggest resecting the rectosigmoid when a lumen stenosis of over 60% is demonstrated at barium enema or colon CT scan. Do the authors have further information on the indication for bowel surgery in their series? Even if they don't, they should expand on this aspect in the Discussion section. 8. Do the authors know the indications for surgery? Did all the women tried a course of medical treatment before undergoing surgery? Was infertility an indication? Do the authors know how many women were seeking pregnancy before surgery, and how many of them conceived after surgery? 9. Was a standard informed consent regarding the surgical procedure adopted? If this is the case, could the authors include this form as a supplemental material? Did the surgeons justify the indication to undergo laparoscopy based on the notion that safe and effective medical therapy for severe rectovaginal endometriosis is not available (page 21)? 10. The authors state that "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" (pages 4, article summary, and 15 and 16). Refractory to what?

	Did all the patients try long-term progestin treatment before undergoing surgery because of pain "refractory" to hormonal medications? If all the patients were non-responders to medical treatment, this should be made explicit and included among the selection criteria. If this is not the case, the word "refractory" should be deleted. Moreover, a comparative effectiveness trial including surgery as experimental treatment and progestin therapy as standard reference treatment is exactly what patients with severely symptomatic endometriosis would need. Thus, the phrase should be modified. I agree that not many women would agree to be randomly allocated to such different treatments, but for the opposite reason, as most of them would prefer to try medical treatment first, and undergo demanding surgery only in case of failure (Vercellini et al., "You can't always get what you want": from doctrine to practicability of study designs for clinical investigation in endometriosis. BMC Womens Health. 2015 Oct 22;15:89). These issue should be addressed under the subheading "Unanswered questions and future research" (page 19). 11. The authors correctly state that pain at intercourse is the symptom typically associated with rectovaginal endometriosis (page 18). In the opinion of this reviewer, in women not seeking pregnancy, severe deep dyspareunia not responding to medical treatment is the most valid indication for this type of surgery. In fact, patients rarely request surgery only because of dyschezia, and dysmenorrhoea is readily relieved by amenorrhoea induced by different medical treatments. This point should be expanded in the Discussion section. 12. Please delete the text at page 19, lines 27-33, as such type of study, being unethical is unfeasible. 13. The prevalence of the "endometriotic disease" is overestimated, and three studies conducted on the general population of reproductive age reported figures ranging from 1% to 3% (Ballard et al., BJOG 2008; Gylfason et al., Am J Epidemiol 2010; Eisenberg et al., BJOG 2017). Thus, please remove the phrase "the high disease prevalence" from the Introduction (page 5). Remove also the details regarding the economic impact of the disease, as estimates could be different between countries with different health care systems. 14. Page 7. Is the scale used to measure several symptoms a 10-point scale (0 to 9), or a 11-point scale (0 to 10)? Zero is a point. 15. According to the STROBE statement, a flow diagram is suggested and should be included in the manuscript. Also a Table showing the demographic and clinical characteristics of the study population would help the reader. In conclusion, this report is based on a very important collaborative study and, if published, could become a reference for the entire endometriosis community. The observed findings will inform patients' choices and guide health care policy makers. The authors should clarify those aspects that could help put their results in the right perspective.

	Given the high number of participating centres and the unprecedented number of patients included, not every detail may be known and, in my view, this may not constitute a major problem, provided this is openly declared, clearly specifying which piece of information is missing. The British Society for Gynaecological Endoscopy has done a very good job. However, because of some study drawbacks, the style should be less skewed in favour of surgery, and the authors should be more cautious when stating that surgery is the only mean to deal with rectovaginal endometriosis. In fact, this study does not provide evidence regarding the purported inefficacy of medical therapy. Moreover, there is an aboundant body of published data clearly demonstrating the benefit of hormonal medications for deep infiltrating endometriosis. Please find a list of some studies on the effectiveness of medical treatments for rectovaginal endometriosis at the end of this review. Interestingly, most of the articles comes from centres known for the high degree of surgical competence in deep endometriosis excision (e.g., Bologna and Genoa). Moreover, one study specifically compared the effects of surgery and progestin treatment for endometriosis-associated severe deep dyspareunia (Vercellini et al., Hum Reprod 2012 and 2013). Somewhat surprisingly, none of the several published studies on progestins for rectovaginal endometriosis has been cited. A balanced and fair approach to the most severe endometriosis form is respectful of patients and would not belittle the role of surgery. With the listed exceptions, surgery is and always should be a choice between two alternatives, and women must not be denied their right to decide. REFERENCES - MEDICAL TREATMENT FOR RECTOVAGINAL ENDOMETRIOSIS Fedele L, Bianchi S, Zanconato G, Portuese A, Raffaelli R. Use of a levonorgestrel-releasing intrauterine device in the treatment of rectovaginal endometriosis. Fertil Steril 2001;75:485–488. Ferrari S, Persico P, DI Puppo F, Vigano P, Tandoi I, Garavaglia E, et al. Continuous low-dose oral contraceptive in the treatment of colorectal endometriosis evaluated by rectal endoscopic ultrasonography. Acta Obstet Gynecol Scand. 2012;91:699-703. Ferrero S, Camerini G, Ragni N, Venturini PL, Biscaldi E, Remorgida V. Norethisterone acetate in the treatment of colorectal endometriosis: a pilot study. Hum Reprod. 2010;25:94-100. Ferrero S, Camerini G, Ragni N, Venturini PL, Biscaldi E, Seracchioli R, et al. Letrozole and norethisterone acetate in colorectal endometriosis. Eur J Obstet Gynecol Reprod Biol. 2010;150:199-202. Ferrero S, Tramalloni D, Venturini PL, Remorgida V. Vaginal danazol for women with rectovaginal endometriosis and pain symptoms persisting after insertion of a levonorgestrel-releasing intrauterine device. Int J Gynaecol Obstet. 2011;113:116-9.

Ferrero S, Leone Roberti Maggiore U, Scala C, di Luca M, Venturini PL, Remorgida V. Changes in the size of rectovaginal endometriotic nodules infiltrating the rectum during hormonal therapies. Arch Gynecol Obstet 2013;287:447–53.

Igarashi M, Iizuka M, Yumiko A, Ibuki Y. Novel vaginal danazol ring therapy for pelvic endometriosis, in particular deeply infiltrating endometriosis. Hum Reprod 1998;13:1952–1956.

Leonardo-Pinto JP, Benetti-Pinto CL, Cursino K, Yele DA. Dienogest and deep infiltrating endometriosis: The remission of symptoms is not related to endometriosis nodule remission. Eur J Obstet Gynecol Reprod Biol 2017; 211:108-111.

Leone Roberti Maggiore U, Remorgida V, Scala C, Tafi E, Venturini PL, Ferrero S. Desogestrel-only contraceptive pill versus sequential contraceptive vaginal ring in the treatment of rectovaginal endometriosis infiltrating the rectum: a prospective open-label comparative study. Acta Obstet Gynecol Scand 2014;93:239–47.

Mabrouk M, Frascà C, Geraci E, Montanari G, Ferrini G, Raimondo D, Alvisi S, et al. Combined oral contraceptive therapy in women with posterior deep infiltrating endometriosis. J Minim Invasive Gynecol. 2011;18:470-4.

Morotti M, Venturini PL, Biscaldi E, Racca A, Calanni L, Vellone VG, et al. Efficacy and acceptability of long-term norethindrone acetate for the treatment of rectovaginal endometriosis. Eur J Obstet Gynecol Reprod Biol 2017;213:4-10.

Razzi S, Luisi S, Calonaci F, Altomare A, Bocchi C, Petraglia F. Efficacy of vaginal danazol treatment in women with recurrent deeply infiltrating endometriosis. Fertil Steril 2007;88:789–794.

Remorgida V, Abbamonte HL, Ragni N, Fulcheri N, Ferrero S. Letrozole and norethisterone in rectovaginal endometriosis. Fertil Steril 2007;88:724–726.

Vercellini P, Pietropaolo G, De giorgi O, Pasin R, Chiodini A, Crosignani PG. Treatment of symptomatic rectovaginal endometriosis with an estrogen–progestogen combination versus low-dose norethindrone acetate. Fertil Steril 2005;84:1375–1387.

Vercellini P, Barbara G, Somigliana E, Bianchi S, Abbiati A, Fedele L. Comparison of
contraceptive ring and patch for the treatment of symptomatic endometriosis. Fertil Steril 2010;93:2150–61.

Vercellini P, Somigliana E, Consonni D, et al. Surgical versus medical treatment for endometriosis-associated severe deep dyspareunia: I. Effect on pain during intercourse and patient satisfaction. Hum Reprod 2012;27:3450–3459.

Vercellini P, Frattaruolo MP, Somigliana E, et al. Surgical versus low-dose progestin treatment for endometriosis-associated severe deep dyspareunia II: effect on sexual functioning, psychological status and health-related quality of life. Hum Reprod 2013;28:1221–1230.

	Vercellini P, Bracco B, Mosconi P, Roberto A, Alberico D, Dhouha D, et al. Norethindrone acetate or dienogest for the treatment of symptomatic endometriosis: a before and after study. Fertil Steril 2016;105:734-43.e3.

REVIEWER	Jason Abbott School of Women's and Children's Health UNSW, Sydney Australia
REVIEW RETURNED	26-Jun-2017

GENERAL COMMENTS	Laparoscopic excision of deep rectovaginal endometriosis in BSGE Endometriosis Centres: A multicentre prospective cohort study of over 5,000 women This is a prospective longitudinal study of 4721 women having laparoscopic excision of deep pelvic endometriosis in and around the rectum. There are excellent operative data including complications for the cohort. Women were followed at 6,12 and 24 months with diminishing numbers for these follow-up data sets regarding clinical outcomes, pain scores, quality of life and analgesic usage. The paper contains important information regarding safety and complications in a very large dataset and this is the most valuable component of the paper. The remaining data are sound, but suffer from large attrition rates, common to database studies and provide some evidence for outcomes up to two years. The paper is generally well-written, however there are several areas that the authors may consider to improve this manuscript. Title: 1. The dataset is on less than 5000 women and this should be reflected in the title. Whilst the pool of women is more than 5000, the authors imposed exclusion criteria reduce this to less than the figure in their title and it is not necessary to overstate the number when it is already substantial. Abstract: 1. The fact that the authors only report data at 6 months, rather than the 24 month mark that they note in their methods as the follow-up duration automatically make me question the follow-up rate. 2. There are notations of ‘improvement’ in quality of life, but no data given and this could be a limitation, given that many readers will limit themselves to the abstract. 3. The notation of surgical complications appears last in results, when in fact this is one of the most important outcomes of these data and should appear first. It is also the most complete data. The importance of complications when performing bowel surgery should be emphasised here. 4. This would also invert the conclusion to note that it is the complications data that are the most important aspect of the dataset. Introduction: 1. Sound and appropriate 2. Denotes efficacy of a chronic disease as a primary outcome which is laudable, but as a reader, it sets the scene for wanting long term data.

	Methods 1. This is a database analysis from a nation-wide group of surgical centres offering laparoscopic treatment of endometriosis. 2. Was this part of a wider ethics approved study? Is this standardized care (including QOL data?). Comment should be made. 3. Did women sign informed consent for participation in the study (or just for their surgery as is written on page 7)? 4. Surgical expertise is suggested, although not expressly described (albeit, that is a most difficult exercise, and in fact the external validity is stronger in the setting of inclusive surgical studies rather than exclusive). 5. The time frame is documented, however this expressly limits follow-up to less than 2 years for women treated between January 2015-June 2016 (given a cut-off date of January 2017 for data completion and analyses). 6. The surgical inclusion criteria are appropriate. 7. Is the Likert scale 10 points (1-10) or 11 points (including 0 and denoting 'no pain')? 8. The bowel symptom scale is not using a validated instrument and this limits its external validity. 9. The EQ5D and EQ5Dvas are used as the QoL instruments. Which specific EQ instrument is used? Please state this early in the methods – it is buried currently. 10. Medical treatments are noted dichotomously, with no recording of quantity (noting the difficulty in this data collection and analysis). This is a limitation, since it could be a single dose of a medication (including an opioid) over the preceding time-frame and this has little if any clinical significance. Regular use of medications is a much more important factor for chronic pain issues. 11. Surgical data are reasonably recorded. 12. It is not clear from the methods if histological confirmation of endometriosis was required (and it should be), although this is alluded to in the opening paragraph of the methods. It is noted that there are no cases of malignancy, however given that this is a dataset pertaining to women with endometriosis, it is imperative that this be an entry point. It is particularly important in the situation where 50% of the cohort have had previous surgery for endometriosis (also see later comments on chronicity). 13. I am not completely clear on the methods used for the sensitivity analyses and the paper does not provide any confidence intervals on any data, which is a limitation. Results: 1. The included dataset is a maximum of 4721 women and this should be reflected throughout the paper. 2. The demography of the women are very limited. There are no data regarding BMI, parity, indication for surgery (pain/fertility/both) and these are important factors for endometriosis and may affect results. These should be included. 3. The fact that 50% of the cohort had previous surgery for endometriosis is very important. This could mean that they have had recurrent symptoms (which may impact chronicity); could be diagnostic only and this would be important to know for referral patterns; may have had incomplete surgery (including ablation) and finally may provide an internal comparative group for both symptom recurrence and the possibility of complications in a recurrent surgery group. The authors may have already considered these data, however this is a striking number and needs to be commented upon in this manuscript.

	4. The follow-up data are somewhat erroneous. Why is the expected number of women at 12 months 3977? This is a loss of 744 women from the original cohort and much more than the expected 295 women that would be considered in a 6 month block based on the date range given. A percentage of women included initially with the sensitivity analyses around these data is appropriate. 5. This should follow-on to the remainder of these data and if there is a time-censored approach based on the entry to the database, then this needs to be stated clearly, but if that is the case, I want to know why 50% of the cohort is not available for a 2 year follow-up given a 7 year time range? 6. For the symptom scores, the authors appropriately point out that there is a significant reduction in QOl at 2 years, although this is clinically insignificant at a drop of 4/100. However, if they do this, then they need to apply this equally to the symptom data regarding bowel function, where a median score of 1 (as just one example) at baseline is said to be statistically significantly reduced at 2 years where the median score is 1. It is imperative that they be consistent with this use of statistical and clinical significance and not selective as they currently are. 7. This same comment follows over to the use of the individual parameters of the EQ-5D where the authors have chosen to report the individual scores, rather than the combined validated score that combines the 5 scores to provide a health state score, that is important both as a comparator to baseline, but also no normative population scores – one of the greatest advantages of this QoL instrument. As individual parameters, there is the same problem of median 0 baseline to 0 2 year scores denoted as significant, when a more sensitive scale could be undertaken. 8. The data relating to bowel complications and a 2.5-fold increase in complications for disc resections compared with segmental resections is noted in the table, but not commented on by the authors. Discussion: 1. The authors note the large sample size of this dataset and indeed should be congratulated on this achievement. My personal thought is let the data stand for itself rather than the aggrandisation of one's achievements, since the notation of 'largest' requires a clear outline of the literature search conducted to make that claim. 2. The data is (at least for me), primarily around the safety of the procedure and the complication rate when performed in expert hands. The authors rank the clinical data more highly, however their loss to follow-up, the use of non-validated bowel instruments and the short term maximal follow-up for a chronic disease state are in fact limitations to the clinical data. 3. There are three placebo-controlled randomised studies on excisional treatment of endometriosis and the authors are aware of this and should state this. Two of these RCTs are complete and include women with deep disease with one of these studies having half the cohort with severe disease including deep endometriosis. None of these placebo controlled RCTs shows a difference between severe and mild disease in terms of pain reduction. All of them show a placebo response and this is important when considering long-term outcomes beyond 6 months. The authors should discuss these RCTs – particularly their weaknesses (of which there are several), in relation to deep disease, but this must include a discussion of the biological plausibility that there is a difference in the severity or location of disease on symptom outcome based on published data to date.

	4. The authors note that the data are collected prospectively minimizing data loss, however this is disingenuous, since at 12 months they have already lost 50% of the cohort and this diminishes substantially over time. This is different to smaller cohorts where data are reported with high retention rates to 5 years including pain and QoL data. This is noted further down in the discussion, but again, this is a matter of consistency in the paper – the authors are both wanting and eating cake on this issue. 5. The sensitivity analyses are somewhat limited since the demography do not clearly define the population and the external validity is poor for that reason. Important in this discussion is the fact that 50% of women had previous surgery for endometriosis. The time to repeat surgery, the location of where they had this done (was this a BSGE centre?) and the indication for the repeat are all vital questions in a chronic disease and are not answered. 6. The fact that the mean age of women in this study is 35, with a further 15 years of reproductive life to go does indicate that the 6 month follow-up offers only a short term outcome for what they may expect. Longer term data are available and it is the reintervention rate that is important (how many surgeries can a women with deeply invasive disease expect in her life?). 7. The surgical complication data, which are both important and represent the most complete component of this study are rather ignored and I think are the most valuable component of this dataset and entirely publishable on its own ground.

REVIEWER	Charles E. Miller, MD Charles E. Miller, MD & Associates, USA
REVIEW RETURNED	26-Jun-2017

GENERAL COMMENTS	First of all I want to congratulate the authors on the very well written manuscript entitled “Laparoscopic excision of deep rectovaginal endometriosis in BSGE Endometriosis Centres: A multicentre prospective cohort study of over 5,000 women”. I also want to send kudos to the BSGE in regards to their forward thinking, establishing centers of excellence in endometriosis throughout the country and demanding that data be collected from these centers. Furthermore, I well recognize that this is not only the largest multi-center study regarding deep infiltrative endometriosis, but also offers the longest follow up of this very difficult patient group. With the above in mind, I am sorry to say that at the present time, I do not believe this article is worthy of publication. It appears that the authors attribute much of the patients’ symptoms and successful outcome to the treatment of deep infiltrative rectovaginal endometriosis. This includes bladder symptoms. Yet, nearly 10% of the patients underwent surgery related to the bladder. Furthermore, a large percentage of these patients underwent hysterectomy and had surgical correction of non-deep infiltrative disease throughout the pelvis. Of course, the outcome of this surgery certainly would influence patients’ subsequent quality of life. There appears to be no mention as to post-operative hormonal treatment, which is well recognized to delay symptom recurrence. While I understand great attention in this article has been given to properly vetting post-operative symptoms and patient fall-out, I believe the tables are very confusing to the reader.

	In fact, my junior partner, who also reviewed this manuscript, was terribly confused pouring over the tables. Finally, I think it would be worthwhile further mining the data to see if there was a difference in patient satisfaction depending upon the radicality of the bowel surgery. Editing: There are several misspelled words including: Strengths (page 4) Be consistent with whether you are presenting the % of cases or absolute number of cases first (Page 11) Add coma on Page 15, line 7: “prospectively, minimizing…” Page 15, Line 42 awkward sentence Page 20, line 23 delete “on”

VERSION 1 – AUTHOR RESPONSE

Reviewers' Comments to Author:

Reviewer: 1 - Reviewer Name: Paolo Vercellini

• Competing Interests: Disclosure of intellectual competing interest - I have a different vision on rectovaginal endometriosis management with respect to that of the authors. I am in favour of long-term medical management, and believe that surgery should be reserved for symptomatic patients who do not respond, do not tolerate, or refuse progestins, for those who have contraindications to progestins or who seek a natural conception, and those who have subocclusive bowel lesions or ureteral stenosis causing hydroureteronephrosis.

We are glad that this reviewer has declared his conflict of interest (COI). We believe that some of the criticism from this review can be explained by this COI and may not be objective. We are aware of the publications that the reviewer is quoting. Indeed, we proposed this reviewer because he had published a systematic review of medical treatments for rectovaginal endometriosis. Indeed, this review (cited in our manuscript) showed that there is limited evidence supporting the sustained effectiveness and acceptability of medical therapies in improving the symptoms of rectovaginal endometriosis. It is therefore surprising that this reviewer holds such a prejudice in favour of medical treatment for the most severe form of endometriotic disease.

It should also be noted that most women referred to a specialist BSGE endometriosis centre have been resistant to medical treatment or conservative surgical therapy. The Methods section of the revised manuscript has added further clarification – “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”).

In contrast to this reviewer, in the absence of compelling evidence to support a particular management approach, we advocate the use of both medical and surgical treatment and indeed based upon the results of our cohort we hope to design an RCT comparing medical and laparoscopic surgical management with important outcomes including resolution of pain symptoms, bowel and urinary symptoms and fertility outcomes.

General comment

- Byrne and co-workers conducted a large, multicentre, prospective cohort study on more than four thousands women who underwent laparoscopic surgical excision of rectovaginal endometriosis. At 6-month follow-up pain symptoms and health-related quality of life, as measured with validated scales, greatly improved and remained stable in those women who were followed for up to 2 years.

Response:Thank you

- The manuscript is well written, simple and clear. The study is valuable not only for the large number of women included and the prospective design but, importantly, also because it has been conducted in many hospitals within U.K., thus substantially increasing the generalisability of the results. Indeed, generalisability of surgical outcomes is among the main problems in rectovaginal endometriosis management. The evidence provided has been obtained through well-planned and intense collaborative efforts. The organisers of this study should be commended for what will most likely become the future reference for the definition of the effect of surgery in this technically demanding clinical condition.

Response:Thank you – we have worked extremely hard to develop this multi-centre standard of specialist surgical care and quality assurance for a hugely important health problem through assessment of efficacy and safety outcomes. This comment is gratifying, and provides another opinion that this is a very important paper.

- For this very reason, the authors also take a great responsibility, as many patients with rectovaginal endometriosis will decide whether to undergo surgery or alternative treatments also based on the results here presented and the accompanying comments. Abundant published evidence, including RCTs, does not support the notion that surgery is the only mean to deal with rectovaginal endometriosis (see page 5, "there is limited evidence supporting the sustained effectiveness and acceptability of medical therapies in improving the symptoms of rectovaginal endometriosis"; page 16, "its resistance to conventional medical treatments"; page 21, "in the absence of safe and effective medical therapy").

Response:These selective examples from the medical literature do not state surgery is the only, or even the best, method of treatment; he has viewed them with an inbuilt bias, reflecting his conflict of interest. This reviewer has published a systematic review of limited primary research data on the efficacy of medical treatment for deep infiltrating endometriosis, which we have referenced in our paper. Whilst some evidence of efficacy is provided these data are from small, often observational studies evaluating varying outcomes and assessing eclectic treatments which limits clinical inference. The more effective treatments appear to be gonadotrophin-releasing analogues and this group of drugs are well recognised to be associated with significant morbidity from the oestrogen deficient state they induce. Thus, we agree that in light of the data we have presented to support the potential efficacy and safety of minimally invasive surgery for endometriosis in specialist centres that an RCT comparing such surgical treatment with medical intervention is feasible and urgently needed. We could not identify any RCTs comparing surgical and medical treatments specifically for rectovaginal endometriosis.

Specific comments

1. The definition of rectovaginal endometriosis is unclear. Rectovaginal endometriosis implies the endometriotic infiltration of the posterior vaginal fornix and of the tunica muscularis of the anterior rectal wall. If this is not the case, then many women did not have "rectovaginal endometriosis", but instead endometriosis of the Douglas pouch, such as fibrotic placques or nodules. This has not only semantic, but also surgical implications. In fact, the surgical treatment of real rectovaginal endometriosis necessitates at least vaginal opening and resection, and sometimes low anterior rectal resection. Moreover, the preoperative diagnosis of rectovaginal endometriosis is based on the presence of bluish and reddish nodules at vaginal inspection, on positive biopsies, on vaginal/rectal US findings, and recto-sigmoidoscopy. This does not seem to have been the case here, as only an indirect indicator of deep Douglas pouch lesions has been adopted as a diagnostic criterion, that is, dissection of the para-rectal space. How could the authors be certain that rectovaginal endometriosis has been excised in all the study-patients?

Response: The study describes outcomes for patients that the surgeon considers to have rectovaginal endometriosis (we can define this as disease that is on the rectum and vagina) and involved pararectal dissection for its removal. Interpretation of the results must be made in that context. We are aware of no universally accepted definition of RVE; perhaps the reviewer can reference one?

We do not agree with the reviewer's assertion that only if the disease is visible vaginally can it be called ''rectovaginal endometriosis", because if the disease does not penetrate through to the vaginal surface but is adherent to the vagina within the Pouch of Douglas it is still invading the vaginal walls. In such a case removal may be achieved without opening the vagina.

We agree that clinical examination and / or imaging can be useful in the diagnosis of recto-vaginal endometriosis but accuracy is limited such that the gold standard diagnosis is by laparoscopic inspection, dissection and subsequent histology. Despite our diagnostic work up including intra-operative visual findings it is possible that rectovaginal disease may not have been present and therefore excised in all of the study cohort but it is highly unlikely that this impacted upon anything more than a minority of patients given the characteristic laparoscopic findings. Moreover, in contrast to other small, uncontrolled series of surgical treatment of deep infiltrating endometriosis involving the recto-vaginal septum, we have provided an objective definition of laparoscopic surgical intervention by defining the preliminary requirement to dissect the para-rectal space. This pragmatic inclusion criteria is reproducible and allows standardisation of the surgical approach and definition of the surgical population facilitating the generalisability and applicability of our findings.

Comment: It should also be noted that for BSGE accredited Endocentres to retain accreditation they have to submit annually edited videos of surgical cases and results of histologically examined tissue confirming specimens from the rectovaginal space. There are no other series or institutions that have published such rigorous data backed up by video and pathological evidence making our series unique.

Response: We can only define the risk of complications for cases where the surgeon considers the patient to have rectovaginal endometriosis and the surgery involves dissection of the pararectal space. It cannot be used for other types of disease.

We have thoroughly explained our rationale for defining the study population in the methods sections (subheading 'study population') we state:
"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."

- This is important because the incidence of major complications, including bowel leak, rectovaginal fistula formation, and ureteral lesions is strictly related with the type of lesions removed and with the extension of the surgical excision. Women must be offered a precise estimate of the incidence of major complications for this specific type of procedure, therefore, knowing exactly what was present and what was removed is relevant. In the experience of this reviewer, women take the decision regarding whether to undergo surgery for rectovaginal endometriosis equally on risk and benefit estimates. The eventuality of underestimating risks should be limited.

Response: See the preceding comment. Standardising the nature and site of deep infiltrating endometriosis is problematic as is defining the exact surgical procedure taken which will inevitably depend upon the location and extent of disease. Thus, for pragmatic and methodologically rigorous reasons we took an objective measure of surgery (dissection of the pararectal space)

- The authors state at page 17 that the observed prevalence (incidence?) of complication was relatively low and compared well with published reports. It is difficult to judge this comment, because it is not known whether vaginal lesions were present and if the posterior fornix was opened and excised.

Response: The correct term is incidence not prevalence.

See the preceding responses. The morbidity arising from excision of recto-vaginal endometriosis relates to its geographical location and depth of invasion. We have tried to standardise this definition to enhance the generalisability of our findings and allow the reader to make a judgement within this context. As stated in our earlier response, we do not agree with the reviewer's assertion that only if the disease is visible vaginally can it be called ''rectovaginal endometriosis", because if the disease does not penetrate through to the vaginal surface but is adherent to the vagina within the Pouch of Douglas it is still invading the vaginal walls. In such a case removal may be achieved without opening the vagina. Furthermore, we are sure that the reviewer is aware that few, if any, papers estimating the incidence of rectovaginal endometriosis define the condition based upon "whether vaginal lesions were present and if the posterior fornix was opened and excised". Indeed, his own work has involved reviewing medical treatments which by definition cannot be diagnosed in the way he describes (because this requires surgical excision), diagnosis being based upon second best laparoscopic visualisation or radiographic imaging.

Comment: Some details suggest that not all women had real rectovaginal endometriosis. Page 11, "a rectovaginal nodule was present in 68.6% women"; "there was endometriosis present on the rectum in 54.7% women"; no mention is made regarding vaginal resection; apparently no ureteral-neocystotomy was performed because of ureteral stenosis and this seems surprising given the exceedingly high number of patients; neurogenic bladder atony, a postoperative complication typical of radical rectovaginal endometriosis resection, does not seem to have been reported.
How many patients had a portion of their vagina removed?

Response: See our preceding responses to definition of surgical population. Again the reviewer's view is based on his opinion of what constitutes rectovaginal endometriosis and not the population studied. (In a revised manuscript we could define rectovaginal endometriosis in the paper as 'the surgeons view that the endometriosis involved the rectum and vagina')

An understanding of the prevalence of serious but rare complications from surgery to treat rectovaginal disease is lacking in the absence of published large cohorts with such disease. More precise estimates can only be provided by large surgical data sets from multi-centre studies such as the present one. Whilst this reviewer believes that the population may have included women without rectovaginal disease, we have selected a pragmatic and reproducible definition of our population allowing readers to generalise the findings to their own patients.

Table 6 of our manuscript reports the rate of ureteric injury and bladder injury. Although we report no cases of ureteral-neocystotomy, this should not be considered 'surprising' because the rates of ureteric injury have been unknown with an degree of precision (note - our series provides more precise estimates of ureteric injury rates) and ureteric injury can be managed in other ways including primary repair and stenting. We have stated in our results that "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."

The subjectivity around excision of rectovaginal disease and 'rectovaginal nodules' led us to define inclusion around a more objective, reproducible measure of surgery: dissection of the pararectal space which precedes all cases of rectovaginal nodule excision or excision of rectal endometriosjs. As described in the methods section of the paper, opening of the vagina to remove the endometriosis is recorded on the surgery data, but this group has not been extracted from the whole population as the results in the paper are relevant to any patient with rectovaginal endometriosis that requires pararectal dissection to ensure removal of disease, not simply those where the vagina was opened.

2. Those patients who underwent hysterectomy and/or bilateral oophorectomy before or after the index surgical procedure should be excluded, as this introduces heterogeneity. This study should answer a specific question, i.e., which was the magnitude of the effect of laparoscopic surgery in reproductive age women with their uterus and at least on ovary present, and who underwent a conservative procedure for symptomatic deep endometriosis. This is what most women with these endometriosis forms would like to know. Previous surgery was already performed in more than half of the study population (page 10), and further confounding should be avoided.

Response: In light of the complexity of laparoscopic surgery for rectovaginal endometriosis and the collection of data from BSGE accredited regional centres, it is expected that many women will have already had some form of previous intervention including surgery for endometriosis. Thus, excluding the 55% of our cohort who had undergone prior surgery in other centres would have limited the generalisability and utility of our findings.

Moreover, deep infiltrating endometriosis by its nature alters anatomy and induces adhesions such that confounding from prior surgery on surgical complexity (and subsequent complications / completeness of excision and symptomatic outcomes) is unlikely to be substantial.

Only a minority of women had undergone bilateral oophorectomy (3%) or hysterectomy (5%) prior to index surgery and these data have been explicitly presented in the manuscript (Results section – first paragraph). However, we wanted to estimate the safety and efficacy of laparoscopic surgical excision of symptomatic rectovaginal endometriosis. Thus, our population was women with pain associated with rectovaginal endometriosis and so exclusion of women with prior medical or surgical treatments including oophorectomy or hysterectomy was inappropriate to our research aim.

As part of the index surgery, 15.3% of women had a concomitant hysterectomy but we did not stratify clinical outcomes by whether hysterectomy was performed or not. With a more complete dataset the prognostic impact of concomitant hysterectomy in women with symptomatic deep infiltrating rectovaginal endometriosis and no future fertility desires, could be explored.

3. Importantly, "there were no cases of malignancy in any of the endometriosis specimens" (page 11). This finding is not commented in the Discussion section, but it should, especially considering the very large number of operated women. It is important to know that in rectoveginal endometriosis forms the oncological risk is exceedingly low. When ovarian endometriomas are present, the decision to operate is often taken also based on the potential presence of malignant lesions.

Response: Our population was women with rectovaginal endometriosis and so any comment related to the decision to operate on ovarian endometriomas cannot be extrapolated to our research. We don't agree that the opinion to operate on an endometrioma is often taken based on potential presence of malignant lesions. This represents reviewer's personal opinion.

We reported the absence of malignancy in analysed specimens but have not discussed this in the Discussion section because the prevalence of malignancy was not the focus of our paper. However, if the editors so wish we can refer to this finding in a revised Discussion.

4. Six-month follow-up questionnaires were available for only half of the participants. This seems a low proportion and the authors should explain in more detail the reason(s) for this. The proportion drops to about one third of the patients at 1-year follow-up, and to about one fifth at 2-year follow-up. In general, participants lost to follow-up are considered a subgroup at worse prognosis compared with those continuing the study. The authors addressed this problem by conducting a sensitivity analysis and maintain that the results remained substantially stable during the entire follow-up period even when considering the worst scenario. However, I wonder whether robust conclusions can be drawn on long-term effects of laparoscopic surgery on pain symptoms and health-related quality of life by applying a statistical model, when questionnaires on pain were available in 4,210 women at baseline and in only 729 at 2 years, and questionnaires on health-related quality of life were available in 4041 women at baseline and in only 644 at 2 years (page 11). Obtaining statistical advice may be wise here.

Response: The reviewer is correct that participants lost to follow-up are considered a subgroup at worse prognosis compared with those continuing the study. This concerned us as well and so we performed sensitivity analyses. We have discussed the limitation of our loss to follow up and our sensitivity analyses to try and mitigate for this extensively in the 'Strengths and weaknesses" section of the Discussion where we state:

“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.”

Rectovaginal endometriosis causes substantial morbidity and affects a substantial number of women of reproductive age. Large datasets, as well as long term follow up, post laparoscopic surgical excision of rectovaginal endometriosis are lacking. Thus, despite the loss to follow up, we believe that our large, multicentre data-set adds valuable and valid information to the medical literature to help inform clinicians and patients and direct future research.

5. I could not find information on postoperative use of medical treatments. This seems crucial, as it as been demonstrated repeatedly that long-term medical therapies improve the outcomes and reduce not only symptom, but also lesion recurrence. Those participants who used postoperative medical treatments should be excluded from the analyses, as it would not be possible to discriminate between the effect of surgery and that of medications.

Response: Data to support the notion that long-term ‘medical therapy’ reduces symptoms and lesion recurrence is lacking. Indeed, an RCT is currently ongoing to look at the impact of hormonal treatments upon symptom recurrence following surgery for superficial endometriosis (Pre-empt – see http://www.birmingham.ac.uk/research/activity/mds/trials/bctu/trials/womens/pre-empt/index.aspx). Table 3 in our manuscript shows the statistically significant reductions in analgesic use post-surgery. We felt this to be the most important ‘medical therapy’ to evaluate as it provides an indirect measure of ongoing pain symptoms. In the interests of brevity and focus, we did not present data for use of hormonal treatments as relatively few women were taking hormones post-laparoscopic surgical treatment (OCP, Mirena, GNRH (+/- addback), progestins, aromatase inhibitors and HRT) but we can present these data if the Editors request us to.

6. The authors state that "analgesia use was significantly reduced at six and 24 months post surgery compared to pre-operative levels for all three analgesic types". Analgesic use is considered an indicator of clinically important pain symptom persistence/recurrence. At 6-month follow-up about 60% of women were still using paracetamol (58.8%), about half were using NSAID (48.9%), and 16% were using opiate, with a reduction of, respectively, 16.2%, 20.9%, and 12.0%. Analgesic use slightly increased uring the follow-up period. The authors emphasise that the reduction in analgesic use from baseline figures was statistically significant ("a significant reduction in the need for analgesia supported the findings of an overall reduction in pain symptoms", page 14). However, given the large sample size, even a limited reduction is here statistically significant. I would rather consider that the proportion of women using analgesics during the entire follow-up period is still substantially high, and perplexities may arise on the real effect of surgery when this variable is contemplated. Moreover, this finding seems in contrast with the major reduction in pain scores observed when using the numerical rating scales. The authors should comment on these aspects in the Discussion section.

Response: Our study was not designed to analyse baseline/long-term levels of analgesia but was looking at changes (increase or decrease) that might be associated with surgery. In this case we saw a large relative reduction in analgesia use. Moreover, it is unrealistic that analgesic usage will be eradicated for chronic pain conditions. Indirect measures of clinical outcomes provide some interesting data but the primary outcomes of patient self-reported clinical outcomes are more important. We have discussed the change in analgesia requirements and sustainability post-surgery in both the short and medium term within the Discussion where we state:
“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. “

7. The authors note that "the incidence [of bowel complications] varied according to whether bowel surgery was undertaken and if so, what type of procedure" (page 14). Based on available data and personal experience, I could not agree more. Some post-operative large bowel complications require emergency re-operation, diverting loop ileostomy or colostomy, intensive care unit admission, and may be life-threatening. Therefore, when disc and segmental bowel resection are associated with, respectively, a 9.3% and 3.9% complication rates (page 14), there must be a very good reason to open the recto-sigmoid lumen deliberately.
Fear over potential morbidity from disc or segmental resection of bowel may explain why only 8% (235/2981) women undergoing bowel surgery had the recto-sigmoid lumen opened. This emphasises the need for precise data from large multicentre series like ours pertaining to surgical efficacy and morbidity according to the type of bowel surgery

In my view, the main reason that renders a pre-planned bowel resection mandatory is the presence of sub-occlusive symptoms. In fact, whether it is worthwhile to take such risks only to improve dyschezia, is a decision that should be left to the woman once adequately informed about the incidence and the clinical impact of such complications. In this regard, the phrase "this rate of complications appears to be acceptable" (page 16) is unclear. Only the woman should judge if this rate of complications is acceptable for her, after being informed that colorectal endometriosis is a benign condition, and there is no evidence that lesions systematically progress and cause occlusion when not excised. The same is true for the sentence "justifying the need for effective surgical treatment even if associated with potentially serious complications" (page 20). Again, this should be an individual patient's judgement, not a general judgement made by surgeons.

Response: We agree that patient management should be individualised and counselling should be thorough regarding clinical outcomes and surgical complication rates again highlighting the importance of our data to allow informed patient choice. Future qualitative studies can be conducted pertaining to patient preferences now that more precise quantitative outcome data has been provided from our series.

Some authors suggest resecting the rectosigmoid when a lumen stenosis of over 60% is demonstrated at barium enema or colon CT scan. Do the authors have further information on the indication for bowel surgery in their series? Even if they don't, they should expand on this aspect in the Discussion section.

This indication for disc or segmental resections was not the focus of our study. The study was pragmatic and the decision to undertake a particular type of bowel surgery or not in order to remove rectovaginal disease was left to the discretion of the surgeon

8. Do the authors know the indications for surgery? Did all the women tried a course of medical treatment before undergoing surgery? Was infertility an indication? Do the authors know how many women were seeking pregnancy before surgery, and how many of them conceived after surgery?

Response: The indication for surgery was chronic pelvic pain in association with endometriosis and this has been clarified in the revised manuscript. (Methods now state “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”). Fertility was not an indication but we plan on producing a subsequent paper on fertility outcomes.

9. Was a standard informed consent regarding the surgical procedure adopted? If this is the case, could the authors include this form as a supplemental material? Did the surgeons justify the indication to undergo laparoscopy based on the notion that safe and effective medical therapy for severe rectovaginal endometriosis is not available (page 21)?

Response: The study was pragmatic and the consenting process was left to the discretion of the surgical team. All operations were performed in tertiary referral BSGE accredited Endometriosis Centres for advanced endometriotic disease refractory to medical treatments. Patients who were satisfied with medical treatment alone would not appear in this cohort.

10. The authors state that "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" (pages 4, article summary, and 15 and 16). Refractory to what? Did all the patients try long-term progestin treatment before undergoing surgery because of pain "refractory" to hormonal medications? If all the patients were non-responders to medical treatment, this should be made explicit and included among the selection criteria. If this is not the case, the word "refractory" should be deleted. Moreover, a comparative effectiveness trial including surgery as experimental treatment and progestin therapy as standard reference treatment is exactly what patients with severely symptomatic endometriosis would need. Thus, the phrase should be modified.

Response: I agree that not many women would agree to be randomly allocated to such different treatments, but for the opposite reason, as most of them would prefer to try medical treatment first, and undergo demanding surgery only in case of failure (Vercellini et al., "You can't always get what you want": from doctrine to practicability of study designs for clinical investigation in endometriosis. BMC Womens Health. 2015 Oct 22;15:89). These issue should be addressed under the subheading "Unanswered questions and future research" (page 19).

All operations were performed in tertiary referral BSGE accredited Endometriosis Centres for advanced endometriotic disease refractory to medical treatments (and this has been clarified in the revised manuscript - Methods now state “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”).). whether they be analgesics or hormonal interventions. We have data on medication being taken at consultation but do not have sophisticated data on detail. It is not practicable to achieve this on an observational study of this size. Clearly perfection is always preferable but we are providing the word literature with the closest we can get and it is important data for clinicians and women to be aware about.

Long-term progestin therapy is not a panacea and indeed is ineffective in many women, may be contraindicated and can cause unacceptable side-effects. We would like to design and conduct an RCT comparing laparoscopic surgical treatment for rectovaginal endometriosis with medical treatments but we have made the reasonable prediction that recruitment to such a study may be problematic because by the very nature of the disease and referral to tertiary specialist centres, many women may be reluctant to have prolongation of their medical ineffective treatments or consider new medical treatments. This reviewer demonstrates his bias for medical treatment by assuming that randomisation would not be possible because of women's preferences for ongoing medical treatment. A pilot RCT with a qualitative element would help us understand the real situation and feasibility of any full blown RCT comparing surgery and medical treatment for this complex condition.

The reviewer appears to be under the erroneous assumption that most women in our cohort have undergone surgery without prior medical treatments or that they may have been coerced into surgery.

11. The authors correctly state that pain at intercourse is the symptom typically associated with rectovaginal endometriosis (page 18). In the opinion of this reviewer, in women not seeking pregnancy, severe deep dyspareunia not responding to medical treatment is the most valid indication for this type of surgery. In fact, patients rarely request surgery only because of dyschezia, and dysmenorrhoea is readily relieved by amenorrhoea induced by different medical treatments. This point should be expanded in the Discussion section.

Response: We cannot speculate on this viewpoint from the data our study has provided.

12. Please delete the text at page 19, lines 27-33, as such type of study, being unethical is unfeasible.

Response: We didn't say that such an RCT was unethical rather that is could be difficult ethically to perform sham incisions and a placebo diagnostic laparoscopy.

13. The prevalence of the "endometriotic disease" is overestimated, and three studies conducted on the general population of reproductive age reported figures ranging from 1% to 3% (Ballard et al., BJOG 2008; Gylfason et al., Am J Epidemiol 2010; Eisenberg et al., BJOG 2017). Thus, please remove the phrase "the high disease prevalence" from the Introduction (page 5). Remove also the details regarding the economic impact of the disease, as estimates could be different between countries with different health care systems.

Response: Pelvic pain and endometriosis accounts for a substantial proportion of referrals to gynaecological clinics and causes substantial morbidity. Disease prevalence varies according to the population and study design. The ESHRE endometriosis guideline which we have cited in the Introduction states that "The exact prevalence of endometriosis is unknown but estimates range from 2 to 10% of women of reproductive age, to 50% of infertile women (Eskenazi and Warner, 1997; Meuleman et al., 2009)." Thus, higher disease prevalence's have also been reported than the reviewer proposes. However, in light of the uncertainty around exact disease prevalence we have removed the phrase 'high disease prevalence'. The reference to economic costs is explicitly stated as relating to the US allowing the reader to form their own relative conclusions from observations within their own health care systems. This illustrates the economic costs in another developed country.

14. Page 7. Is the scale used to measure several symptoms a 10-point scale (0 to 9), or a 11-point scale (0 to 10)? Zero is a point.

Response: We have revised the manuscript (as Reviewer 2 raised the same point) to state a "Likert scale from 0-10" rather than 10-point scale if this provides further clarification.

15. According to the STROBE statement, a flow diagram is suggested and should be included in the manuscript. Also a Table showing the demographic and clinical characteristics of the study population would help the reader.

Response: We have submitted a completed STROBE statement and this can be included as supplementary material. We did not collect details of demography other than age.

In conclusion, this report is based on a very important collaborative study and, if published, could become a reference for the entire endometriosis community. The observed findings will inform patients' choices and guide health care policy makers. The authors should clarify those aspects that could help put their results in the right perspective. Given the high number of participating centres and the unprecedented number of patients included, not every detail may be known and, in my view, this may not constitute a major problem, provided this is openly declared, clearly specifying which piece of information is missing.

The British Society for Gynaecological Endoscopy has done a very good job. However, because of some study drawbacks, the style should be less skewed in favour of surgery, and the authors should be more cautious when stating that surgery is the only mean to deal with rectovaginal endometriosis. In fact, this study does not provide evidence regarding the purported inefficacy of medical therapy. Moreover, there is an aboundant body of published data clearly demonstrating the benefit of hormonal medications for deep infiltrating endometriosis. Please find a list of some studies on the effectiveness of medical treatments for rectovaginal endometriosis at the end of this review. Interestingly, most of the articles comes from centres known for the high degree of surgical competence in deep endometriosis excision (e.g., Bologna and Genoa). Moreover, one study specifically compared the effects of surgery and progestin treatment for endometriosis-associated severe deep dyspareunia (Vercellini et al., Hum Reprod 2012 and 2013). Somewhat surprisingly, none of the several published studies on progestins for rectovaginal endometriosis has been cited.

A balanced and fair approach to the most severe endometriosis form is respectful of patients and would not belittle the role of surgery. With the listed exceptions, surgery is and always should be a choice between two alternatives, and women must not be denied their right to decide.

Please see our initial concerns pertaining to this reviewer’s partiality regarding the relative roles of surgery and medical treatment. Furthermore, whilst he recognises the unprecented size and multi-centre nature of our surgical series, he is requesting a level of detailed information that our series is not sensitive enough to answer. It is unlikely that such a large series (for example published papers from large data-sets derived from the UK Department of Health HRG groups) can ever provide the level of detail requested here. Smaller scale longitudinal and qualitative studies would be required to provide such data.

Also see our specific responses to individual points. The focus of our study has been to report the efficacy and safety of laparoscopic surgery for rectovaginal endometriosis. We have not evaluated medical treatments nor have we tried to compare the effect of medical treatment with surgical treatment. We have cited three studies pertaining to the use of medical treatments in our Introduction including a systematic review published in 2009 by this reviewer. The studies cited by him comparing the effects of progestins and surgery were prone to bias (small, non-randomised studies open to selection bias, with differential rates of follow up) and of limited generalisability being restricted to evaluating narrow clinical outcomes. Indeed, his own review (of small generally observational, non-comparative studies) concludes: “…… conclusions are limited by the paucity of published reports, the limited quality of the evidence presented in the non-comparative studies, the small numbers of subjects included in most trials, and the inherent risk of several types of biases. In particular,

publication bias may constitute a major drawback, especially when considering case series, which are more prone to over-represent optimistic results. Moreover, several drugs have been used, with various modalities of administration, different dosages and diverse periods of treatment. In addition, therapies were occasionally combined, thus preventing assessment of the effect of specific medications."

We have made explicit in our Discussion section the need for RCTs including those comparing surgical and non-surgical treatments. Thus, this reviewer should be reassured that we are not presenting a one-sided treatise for surgery but rather reporting the surgical outcome data from a large data-set from multiple specialist centres for a complex and enigmatic disease which can cause prolonged misery for those suffering with it.

REFERENCES - MEDICAL TREATMENT FOR RECTOVAGINAL ENDOMETRIOSIS

Fedele L, Bianchi S, Zanconato G, Portuese A, Raffaelli R. Use of a levonorgestrel-releasing intrauterine device in the treatment of rectovaginal endometriosis. Fertil Steril 2001;75:485–488.

Ferrari S, Persico P, DI Puppo F, Vigano P, Tandoi I, Garavaglia E, et al. Continuous low-dose oral contraceptive in the treatment of colorectal endometriosis evaluated by rectal endoscopic ultrasonography. Acta Obstet Gynecol Scand. 2012;91:699-703.

Ferrero S, Camerini G, Ragni N, Venturini PL, Biscaldi E, Remorgida V. Norethisterone acetate in the treatment of colorectal endometriosis: a pilot study. Hum Reprod. 2010;25:94-100.

Ferrero S, Camerini G, Ragni N, Venturini PL, Biscaldi E, Seracchioli R, et al. Letrozole and norethisterone acetate in colorectal endometriosis. Eur J Obstet Gynecol Reprod Biol. 2010;150:199-202.

Ferrero S, Tramalloni D, Venturini PL, Remorgida V. Vaginal danazol for women with rectovaginal endometriosis and pain symptoms persisting after insertion of a levonorgestrel-releasing intrauterine device. Int J Gynaecol Obstet. 2011;113:116-9.

Ferrero S, Leone Roberti Maggiore U, Scala C, di Luca M, Venturini PL, Remorgida V. Changes in the size of rectovaginal endometriotic nodules infiltrating the rectum during hormonal therapies. Arch Gynecol Obstet 2013;287:447–53.

Igarashi M, Iizuka M, Yumiko A, Ibuki Y. Novel vaginal danazol ring therapy for pelvic endometriosis, in particular deeply infiltrating endometriosis. Hum Reprod 1998;13:1952–1956.

Leonardo-Pinto JP, Benetti-Pinto CL, Cursino K, Yele DA. Dienogest and deep infiltrating endometriosis: The remission of symptoms is not related to endometriosis nodule remission. Eur J Obstet Gynecol Reprod Biol 2017; 211:108-111.

Leone Roberti Maggiore U, Remorgida V, Scala C, Tafi E, Venturini PL, Ferrero S. Desogestrel-only contraceptive pill versus sequential contraceptive vaginal ring in the treatment of rectovaginal endometriosis infiltrating the rectum: a prospective open-label comparative study. Acta Obstet Gynecol Scand 2014;93:239–47.

Mabrouk M, Frascà C, Geraci E, Montanari G, Ferrini G, Raimondo D, Alvisi S, et al. Combined oral contraceptive therapy in women with posterior deep infiltrating endometriosis. J Minim Invasive Gynecol. 2011;18:470-4.

Morotti M, Venturini PL, Biscaldi E, Racca A, Calanni L, Vellone VG, et al. Efficacy and acceptability of long-term norethindrone acetate for the treatment of rectovaginal endometriosis. Eur J Obstet Gynecol Reprod Biol 2017;213:4-10.

Razzi S, Luisi S, Calonaci F, Altomare A, Bocchi C, Petraglia F. Efficacy of vaginal danazol treatment in women with recurrent deeply infiltrating endometriosis. Fertil Steril 2007;88:789–794.

Remorgida V, Abbamonte HL, Ragni N, Fulcheri N, Ferrero S. Letrozole and norethisterone in rectovaginal endometriosis. Fertil Steril 2007;88:724–726.

Vercellini P, Pietropaolo G, De giorgi O, Pasin R, Chiodini A, Crosignani PG. Treatment of symptomatic rectovaginal endometriosis with an estrogen–progestogen combination versus low-dose norethindrone acetate. Fertil Steril 2005;84:1375–1387.

Vercellini P, Barbara G, Somigliana E, Bianchi S, Abbiati A, Fedele L. Comparison of contraceptive ring and patch for the treatment of symptomatic endometriosis. Fertil Steril 2010;93:2150–61.

Vercellini P, Somigliana E, Consonni D, et al. Surgical versus medical treatment for endometriosis-associated severe deep dyspareunia: I. Effect on pain during intercourse and patient satisfaction. Hum Reprod 2012;27:3450–3459.

Vercellini P, Frattaruolo MP, Somigliana E, et al. Surgical versus low-dose progestin treatment for endometriosis-associated severe deep dyspareunia II: effect on sexual functioning, psychological status and health-related quality of life. Hum Reprod 2013;28:1221–1230.

Vercellini P, Bracco B, Mosconi P, Roberto A, Alberico D, Dhouha D, et al. Norethindrone acetate or dienogest for the treatment of symptomatic endometriosis: a before and after study. Fertil Steril 2016;105:734-43.e3.

Reviewer: 2
Reviewer Name: Jason Abbott
Institution and Country: School of Women's and Children's Health UNSW, Sydney, Australia
Competing Interests: none declared

This is a prospective longitudinal study of 4721 women having laparoscopic excision of deep pelvic endometriosis in and around the rectum. There are excellent operative data including complications for the cohort. Women were followed at 6,12 and 24 months with diminishing numbers for these follow-up data sets regarding clinical outcomes, pain scores, quality of life and analgesic usage. The paper contains important information regarding safety and complications in a very large dataset and this is the most valuable component of the paper. The remaining data are sound, but suffer from large attrition rates, common to database studies and provide some evidence for outcomes up to two years. The paper is generally well-written, however there are several areas that the authors may consider to improve this manuscript.

Title:

1. The dataset is on less than 5000 women and this should be reflected in the title. Whilst the pool of women is more than 5000, the authors imposed exclusion criteria reduce this to less than the figure in their title and it is not necessary to overstate the number when it is already substantial.

Response: We have changed the title in the revised manuscript with no reference to the sample size – "Laparoscopic excision of deep rectovaginal endometriosis in BSGE Endometriosis Centres: A multicentre prospective cohort study"

Abstract:

1. The fact that the authors only report data at 6 months, rather than the 24 month mark that they note in their methods as the follow-up duration automatically make me question the follow-up rate.

Response: We already note in the abstract that improvements are maintained/sustained at 2 years. although 12 and 24 month data have not been presented in the abstract because of word count restriction (we can add 12 and 24 month data if requested by the Editors. Follow up and attrition rates at 12 and 24 months are reported and our handling of the uncertainty around missing follow up data (sensitivity analyses) are reported and discussed.

2. There are notations of 'improvement' in quality of life, but no data given and this could be a limitation, given that many readers will limit themselves to the abstract.

Response: The data from the EuroQol 5D and VAS are presented in Tables 2,4 and 5 and under "Symptom outcomes" in the Results section. Furthermore, the abstract provides median quality of life scores pre-operatively and at 6 months.

3. The notation of surgical complications appears last in results, when in fact this is one of the most important outcomes of these data and should appear first. It is also the most complete data.

Response: The importance of complications when performing bowel surgery should be emphasised here.
For consistency throughout the manuscript (Abstract, Methods and Results sections) we have presented the symptomatic outcomes before surgical complications

4. This would also invert the conclusion to note that it is the complications data that are the most important aspect of the dataset.

Response: We disagree. Complications are important but the acceptability or otherwise of surgical morbidity can only be judged in the context of symptomatic outcomes and vice versa.

Introduction:

1. Sound and appropriate

Response: Thank you

2. Denotes efficacy of a chronic disease as a primary outcome which is laudable, but as a reader, it sets the scene for wanting long term data.

Response: We have provided 6, 12 and 24 month data

Methods

1. This is a database analysis from a nation-wide group of surgical centres offering laparoscopic treatment of endometriosis.

Response: Yes

2. Was this part of a wider ethics approved study? Is this standardized care (including QOL data?). Comment should be made.

Response: No it was not, otherwise it would have been stated. 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. We have stated that this study describes care actually received in over 50 hospitals – we have revised the manuscript to clarify that treatment decisions were made by individual clinicians and individual patients, and they were not prescribed by the study.

3. Did women sign informed consent for participation in the study (or just for their surgery as is written on page 7)?

Response: For participation in the study. This is explained in study population paragraph line three, page 4 of doc…. ' and gave written consent for data collection'.. See response above also.

4. Surgical expertise is suggested, although not expressly described (albeit, that is a most difficult exercise, and in fact the external validity is stronger in the setting of inclusive surgical studies rather than exclusive).

Response: We agree – generalisability is enhanced by the multi-centre nature of our study. All centres were accredited by the BSGE; provisional status is granted initially before accreditation - to acquire and retain full BSGE accreditation, Endocentres are audited annually on surgical workload data completion and completeness of follow up, they are also required to submit annually edited videos of surgical exemplar cases for review by the scientific advisory group to confirm examples of the cases undergoing surgery. There are no other series or institutions that have published such rigorous data backed up by video and pathological evidence making our series unique.

Furthermore, 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, to avoid selection bias.

5. The time frame is documented, however this expressly limits follow-up to less than 2 years for women treated between January 2015-June 2016 (given a cut-off date of January 2017 for data completion and analyses).

Response: We agree. However, as we are presenting surgical technique and complication data in addition to clinical outcome data, we took a pragmatic decision to include women who could only provide truncated symptomatic outcome data. The alternative approach would have been to restrict data analysis to women operated upon by January 2015 but we chose to provide the totality of available data and as this reviewer has alluded to, surgical morbidity data is of great importance, hence our decision to provide the most data possible.

6. The surgical inclusion criteria are appropriate.

Response: Thank you

7. Is the Likert scale 10 points (1-10) or 11 points (including 0 and denoting 'no pain')?

Response: Reviewer one alluded to this – we have clarified the revised manuscript which now says: "All patients recorded their clinical symptoms on a BSGE standard questionnaire using a 0-10 point Likert scale ……"

8. The bowel symptom scale is not using a validated instrument and this limits its external validity.

Response: We agree, our scale has not been psychometrically tested. However, validated instruments do not exist for our population (in contrast to say evaluating irritable bowel syndrome). The data we provide are germane to the symptoms our patients with endometriosis complain of and as such has face validity.

9. The EQ5D and EQ5Dvas are used as the QoL instruments. Which specific EQ instrument is used? Please state this early in the methods – it is buried currently.

Response: The EuroQol instrument is explicitly stated and referenced in the Methods section which states: "Patient reported quality of life data were collected using EuroQuol 5D questionnaire and EuroQuol Visual Analogue Score.17,18"

10. Medical treatments are noted dichotomously, with no recording of quantity (noting the difficulty in this data collection and analysis). This is a limitation, since it could be a single dose of a medication (including an opioid) over the preceding time-frame and this has little if any clinical significance. Regular use of medications is a much more important factor for chronic pain issues.

Response: We agree that dichotomizing data does reduced sensitivity. However, as this reviewer has conceded, multi-centre, large databases requiring patient time and understanding to input data, cannot practically be achieved if overly extensive and detailed data are required. It is a balance between compliance with data input (completion of follow up) and ideal information gathering. Pragmatism is required and restriction of data input to the most important outcome data and ease of data entry.

11. Surgical data are reasonably recorded.

Response: Thank you

12. It is not clear from the methods if histological confirmation of endometriosis was required (and it should be), although this is alluded to in the opening paragraph of the methods. It is noted that there are no cases of malignancy, however given that this is a dataset pertaining to women with endometriosis, it is imperative that this be an entry point. It is particularly important in the situation where 50% of the cohort have had previous surgery for endometriosis (also see later comments on chronicity).

Response: Histological data were not an inclusion criteria or outcome of this study but histology of all removed specimens was recorded for evidence of malignant transformation. This has been explicitly stated in the manuscript (Methods and Results).

13. I am not completely clear on the methods used for the sensitivity analyses and the paper does not provide any confidence intervals on any data, which is a limitation.

Response: The methods used for both sensitivity analyses are explicitly and comprehensively stated in the manuscript under “Statistical methods” in the Methods section and under “Sensitivity analyses” in the Results section and discussed within the ‘Discussion section”. We can include a diagram to explain the sensitivity analysis more clearly if and include quartiles or confidence intervals if requested by the Editors.

Results:
1. The included dataset is a maximum of 4721 women and this should be reflected throughout the paper.
The denominators are made clear throughout the analysis. The title of the paper has been changed to remove the sample size (see response to first point)

2. The demography of the women are very limited. There are no data regarding BMI, parity, indication for surgery (pain/fertility/both) and these are important factors for endometriosis and may affect results. These should be included.
The database input criteria were updated in 2015 to collect data on BMI and fertility in addition to age. The indication for surgery was some form of chronic pelvic pain in association with rectovaginal endometriosis. We have clarified this in the Methods section of the revised manuscript under the subheading “Study design” of the revised manuscript: “A multi-centre prospective cohort study of pre-menopausal women undergoing surgery for pelvic pain associated with rectovaginal disease was performed.”

3. The fact that 50% of the cohort had previous surgery for endometriosis is very important. This could mean that they have had recurrent symptoms (which may impact chronicity); could be diagnostic only and this would be important to know for referral patterns; may have had incomplete surgery (including ablation) and finally may provide an internal comparative group for both symptom recurrence and the possibility of complications in a recurrent surgery group. The authors may have already considered these data, however this is a striking number and needs to be commented upon in this manuscript.
In light of the complexity of laparoscopic surgery for rectovaginal endometriosis and the collection of data from tertiary referral BSGE accredited regional centres, it is expected that many women will have already had some form of previous intervention including diagnostic or therapeutic surgery for endometriosis. Most women undergoing previous surgery would have been undertaken in non-specialist centres so the likelihood of this group of women being ‘more diseased’ such that recurrent symptoms and chronicity of symptoms would be more prevalent is unlikely. However, such an analysis would be interesting amongst this subgroup and others but we did not undertake these analyses because (i) we did not design the study to look at these subgroups a priori and (ii) given the loss to follow up the power of any such subgroup analysis would be limited.

4. The follow-up data are somewhat erroneous. Why is the expected number of women at 12 months 3977? This is a loss of 744 women from the original cohort and much more than the expected 295 women that would be considered in a 6 month block based on the date range given. A percentage of women included initially with the sensitivity analyses around these data is appropriate.

The number of endometriosis centres and the number of patients being operated on at each centre rose markedly over the course of the study. We could include the analysis restricted to the first 5 years of data in supplementary tables but we believe that this would this level of complexity may impact upon the readability of the manuscript as well as raise methodological issues associated with unplanned subgroup analyses. Also see later comments pertaining to inappropriate detailed analyses.

5. This should follow-on to the remainder of these data and if there is a time-censored approach based on the entry to the database, then this needs to be stated clearly, but if that is the case, I want to know why 50% of the cohort is not available for a 2 year follow-up given a 7 year time range?
Please refer to our response to the preceding point.

6. For the symptom scores, the authors appropriately point out that there is a significant reduction in QOl at 2 years, although this is clinically insignificant at a drop of 4/100. However, if they do this, then they need to apply this equally to the symptom data regarding bowel function, where a median score of 1 (as just one example) at baseline is said to be statistically significantly reduced at 2 years where the median score is 1. It is imperative that they be consistent with this use of statistical and clinical significance and not selective as they currently are.
We agree that there is a difference between clinical and statistical significance. Qol was a secondary outcome and data are explicitly presented in Table 2. The headline finding is the median improvement in QoL on the VAS from baseline (pre-surgery) of 25 points from 55 to 80/100 at 6 months, 80/100 at 12 months and 76/100 at 24 months. As we have reported in the Table (and selectively identified by the reviewer) the drop in median QoL score at 6 months (80/100) compared with 24 months (76/100) is only 4 points but does represent a statistically significant drop in QoL given our large sample size. Whilst we agree with the reviewer that this drop is of debatable statistical significance, the global inference is that QoL significantly improves both clinically and statistically from baseline to 6 months and is sustained at 12 and 24 months (albeit with a small 4/100 reduction between 6/12 months and 24 months).

We have revised the Results section of the manuscript to address this reviewer's point from:
"In addition, there was a statistically significant reduction in voiding difficulty, bladder pain, bowel frequency, bowel urgency, incomplete bowel emptying, constipation and passing blood in the stool (see table 2)."
to "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 2)."

7. This same comment follows over to the use of the individual parameters of the EQ-5D where the authors have chosen to report the individual scores, rather than the combined validated score that combines the 5 scores to provide a health state score, that is important both as a comparator to baseline, but also no normative population scores – one of the greatest advantages of this QoL instrument. As individual parameters, there is the same problem of median 0 baseline to 0 2 year scores denoted as significant, when a more sensitive scale could be undertaken.
Generic QoL instruments like EuroQol arguably lack sensitivity and relevance to specific disease conditions but do allow comparison across diverse health states. The EQ-5D does encompass a global VAS score which we used to compare health states in addition to the five specific domains. If requested by the Editors we can perform further analyses using a combined QALY index score of the EQ5D to provide further sensitivity and an element of 'normative populations scores'.

8. The data relating to bowel complications and a 2.5-fold increase in complications for disc resections compared with segmental resections is noted in the table, but not commented on by the authors.
We did not feel it appropriate to make inferences about the technique (clinical outcomes and morbidity) used to remove rectovaginal endometriosis given the relatively small numbers of women undergoing procedures involving opening the bowel lumen with a subsequent bowel resection. Only 8% (235/2981) of women undergoing bowel surgery had the recto-sigmoid lumen opened without resection (also it should be noted that the bowel lumen is also opened during segmental resection).

Future studies should be designed to compare the morbidity and outcomes associated with specific surgical approaches.

Discussion:

1. The authors note the large sample size of this dataset and indeed should be congratulated on this achievement. My personal thought is let the data stand for itself rather than the aggrandisation of one's achievements, since the notation of 'largest' requires a clear outline of the literature search conducted to make that claim.

We would generally agree with this sentiment regarding the relative size of studies. However, the current study is so large given its multicentre design that we feel justified in stating that "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." We have undertaken a systematic search of the literature to confirm that no other study of laparoscopic surgery for rectovaginal endometriosis reports such a large data set. The reviewer understands this fact, because he is an expert in endometriosis, but a non-specialist reader may not understand the size of the data in context. If the reviewer could reference a larger dataset then we can adapt this statement, but it is not written for any aggrandisement but to make clear to the reader that it is the largest data set by a considerable margin.If the Editors agree with this reviewer that the statement of fact represents 'self-aggrandisement' then we can remove the sentence.

2. The data is (at least for me), primarily around the safety of the procedure and the complication rate when performed in expert hands. The authors rank the clinical data more highly, however their loss to follow-up, the use of non-validated bowel instruments and the short term maximal follow-up for a chronic disease state are in fact limitations to the clinical data. Complications are important but the acceptability or otherwise of surgical morbidity can only be judged in the context of symptomatic outcomes and vice versa. Obtaining patient reported outcomes (PROMs) is undoubtedly more difficult but generally seen as more clinically relevant than simply reporting feasibility and safety data. Whilst the reviewer as a surgeon may appreciate the objectivity of complication rates, patients will want to know if taking the risk of surgery is justified. So quality of life is the most important outcome for them. We believe that our extensive sensitivity analysis go some way to address the uncertainties arising from any loss to follow up.

3. There are three placebo-controlled randomised studies on excisional treatment of endometriosis and the authors are aware of this and should state this. Two of these RCTs are complete and include women with deep disease with one of these studies having half the cohort with severe disease including deep endometriosis. None of these placebo controlled RCTs shows a difference between severe and mild disease in terms of pain reduction. All of them show a placebo response and this is important when considering long-term outcomes beyond 6 months. The authors should discuss these RCTs – particularly their weaknesses (of which there are several), in relation to deep disease, but this must include a discussion of the biological plausibility that there is a difference in the severity or location of disease on symptom outcome based on published data to date.

The RCTs alluded to by this reviewer were included in the following Cochrane review - Duffy JMN, Arambage K, Correa FJS, Olive D, Farquhar C, Garry R, Barlow DH, Jacobson TZ. Laparoscopic surgery for endometriosis. Cochrane Database of Systematic Reviews 2014, Issue 4. Art. No.: CD011031. DOI: 10.1002/14651858.CD011031.pub2. This review was focused on 'mild and moderate endometriosis' not rectovaginal endometriosis and so the findings are not transferable to this population and hence the importance of our dataset (paucity of literature on rectovaginal endometriosis).

Whilst this reviewers (Abbot et al, 2004) RCT included revised American Fertility Stage (rAFS) classification stage 1-4 (3/4 implying deeper infiltrative disease but not specifically rectovaginal endometriosis) and two other studies included in the review rAFS 1-3, the populations are not relatable and so any inferences from these eclectic populations within subgroups in already small studies will be unreliable.

4. The authors note that the data are collected prospectively minimizing data loss, however this is disingenuous, since at 12 months they have already lost 50% of the cohort and this diminishes substantially over time. This is different to smaller cohorts where data are reported with high retention rates to 5 years including pain and QoL data. This is noted further down in the discussion, but again, this is a matter of consistency in the paper – the authors are both wanting and eating cake on this issue.
In the "Strengths and weaknesses" section of our Discussion we have explicitly discussed the implications of the attrition rates and our attempts to mitigate against these and aid data interpretation in a scientific and non-biased way. Prospective data collection does minimise data loss, especially incomplete data, recall bias and allows consistency of data collection. This is irrefutable. Despite our prospective design, attrition occurred because of the realities of collecting patient reported outcome data.

5. The sensitivity analyses are somewhat limited since the demography do not clearly define the population and the external validity is poor for that reason. Important in this discussion is the fact that 50% of women had previous surgery for endometriosis. The time to repeat surgery, the location of where they had this done (was this a BSGE centre?) and the indication for the repeat are all vital questions in a chronic disease and are not answered.
See previous responses regarding demographic data collection and subgroup analyses. With more complete follow up we could have considered subgroup analyses around disease severity e.g. prior surgery, repeat surgery within a BSGE Endocentre etc. However, we standardised the definition of our population by defining women with chronic pain undergoing laparoscopic surgery for rectovaginal endometriosis requiring dissection of the pararectal space.

We have revised the Discussion (Conclusion) section of the manuscript as requested by this reviewer to discuss the observation that 50% of women had previous surgery for endometriosis. . The revised manuscript states:
"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.".

6. The fact that the mean age of women in this study is 35, with a further 15 years of reproductive life to go does indicate that the 6 month follow-up offers only a short term outcome for what they may expect. Longer term data are available and it is the reintervention rate that is important (how many surgeries can a women with deeply invasive disease expect in her life?).
We have also reported medium term data at 12 and 24 months. Our database is collecting data on an ongoing basis and so data pertaining to surgical re-intervention rates will be available in the future

7. The surgical complication data, which are both important and represent the most complete component of this study are rather ignored and I think are the most valuable component of this dataset and entirely publishable on its own ground.
The reviewer appears to be recognising the importance of these data and endorsing publication. Complications are important but the acceptability or otherwise of surgical morbidity can only be judged in the context of symptomatic outcomes and vice versa. Obtaining patient reported outcomes (PROMs) is undoubtedly more difficult but generally seen as more clinically relevant than simply reporting feasibility and safety data.

Reviewer: 3
Reviewer Name: Charles E. Miller, MD
Institution and Country: Charles E. Miller, MD & Associates, USA
Competing Interests: None declared

First of all I want to congratulate the authors on the very well written manuscript entitled "Laparoscopic excision of deep rectovaginal endometriosis in BSGE Endometriosis Centres: A multicentre prospective cohort study of over 5,000 women". I also want to send kudos to the BSGE in regards to their forward thinking, establishing centers of excellence in endometriosis throughout the country and demanding that data be collected from these centers. Furthermore, I well recognize that this is not only the largest multi-center study regarding deep infiltrative endometriosis, but also offers the longest follow up of this very difficult patient group.

Thank you – this reviewer has recognised the large size of the study (no 'self-aggrandisement') and the length of follow up.

With the above in mind, I am sorry to say that at the present time, I do not believe this article is worthy of publication. It appears that the authors attribute much of the patients' symptoms and successful outcome to the treatment of deep infiltrative rectovaginal endometriosis. This includes bladder symptoms. Yet, nearly 10% of the patients underwent surgery related to the bladder. Furthermore, a large percentage of these patients underwent hysterectomy and had surgical correction of non-deep infiltrative disease throughout the pelvis. Of course, the outcome of this surgery certainly would influence patients' subsequent quality of life.

The population definition is clearly described (in contrast to most other studies of surgery for rectovaginal endometriosis). The presence of endometriotic disease beyond rectovaginal disease did not preclude inclusion in the study and surgical excision was performed for all identifiable disease e.g. bladder, ovary etc. (and data collected) and the exact approach left to the discretion of the operating surgical team. The varying distribution of endometriosis within the pelvis reflects the heterogeneity of the disease.

As part of the index surgery, only 15.3% of women had a concomitant hysterectomy but we did not stratify clinical outcomes by whether hysterectomy was performed or not. With a more complete dataset the prognostic impact of concomitant hysterectomy in women with symptomatic deep infiltrating rectovaginal endometriosis and no future fertility desires, could be explored.

There appears to be no mention as to post-operative hormonal treatment, which is well recognized to delay symptom recurrence.

Data to support the notion that long-term 'medical therapy' reduces symptoms and lesion recurrence is lacking. Indeed, an RCT is currently ongoing to look at the impact of hormonal treatments upon symptom recurrence following surgery for superficial endometriosis (Pre-empt – see). Table 3 in our manuscript shows the statistically significant reductions in analgesic use post-surgery. We felt this to be the most important 'medical therapy' to evaluate as it provides an indirect measure of ongoing pain symptoms. We did not present data for use of hormonal treatments as relatively few women were taking hormones post-laparoscopic surgical treatment but we can present these data if the Editors request us to.

While I understand great attention in this article has been given to properly vetting post-operative symptoms and patient fall-out, I believe the tables are very confusing to the reader. In fact, my junior partner, who also reviewed this manuscript, was terribly confused pouring over the tables.
The tables are succinct and interpretable to our mind so we are surprised to receive this comment particularly as the other reviewers reported well-written and clear paper with no negative comment about tables. We are happy for the Editors to arbitrate on the clarity of the tables.

Finally, I think it would be worthwhile further mining the data to see if there was a difference in patient satisfaction depending upon the radicality of the bowel surgery.

We did not feel it appropriate to make inferences about the specific technique (clinical outcomes and morbidity) used to remove rectovaginal endometriosis from the bowel given the relatively small numbers of women undergoing procedures involving opening the bowel lumen.
Only 8% (235/2981) women undergoing bowel surgery had the recto-sigmoid lumen opened. Future studies should be designed to compare the morbidity and outcomes associated with specific surgical approaches and with more data collection we hope to be able to add to the current evidence base regarding the radicality of surgery in future.

Editing:
There are several misspelled words including: Strengths (page 4)
Spelling corrected in the revised manuscript
Be consistent with whether you are presenting the % of cases or absolute number of cases first (Page 11)
Consistency confirmed
Add coma on Page 15, line 7: “prospectively, minimizing…”
Comma added in the revised manuscript
Page 20, line 23 delete “on”
We are happy with the grammar – no change

VERSION 2 – REVIEW

REVIEWER	Paolo Vercellini Department of Clinical Sciences and Community Health and Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Milano, Italy Disclosure of intellectual competing interest - I have a different vision on rectovaginal endometriosis management with respect to that of the authors. I am in favour of long-term medical management, and believe that surgery should be reserved for symptomatic patients who do not respond, do not tolerate, or refuse progestins, for those who have contraindications to progestins or who seek a natural conception, and those who have subocclusive bowel lesions or ureteral stenosis causing hydroureteronephrosis.
REVIEW RETURNED	07-Oct-2017

GENERAL COMMENTS	In their Response to Reviewers the authors have addressed my comments, but modifications included in the manuscript are very limited. They maintain "Indeed, we proposed this reviewer because he had published a systematic review of medical treatments for rectovaginal endometriosis", and "It is therefore surprising that this reviewer holds such a prejudice in favour of medical treatment for the most severe form of endometriotic disease". It is not a prejudice, it is the result of decades of clinical research and experience of our centre. We would have not insisted on this aspect of management had we not observed satisfactory results with hormonal therapies. Several reports have been published after our review confirming the effectiveness of medical treatment for deep endometriosis, including rectovaginal, bowel, and bladder forms. As a consequence, if I were a co-author of this paper, I would have avoided any comment on the purported inefficacy of hormonal treatments for rectovaginal endometriosis, also because the data provided do not allow any meaningful additional conclusion on this point (see page 5, "there is limited evidence supporting the sustained effectiveness and acceptability of medical therapies in improving the symptoms of rectovaginal endometriosis"; page 16, "its resistance to conventional medical treatments"; page 21, "in the absence of safe and effective medical therapy"). The authors state "In contrast to this reviewer, in the absence of compelling evidence to support a particular management approach, we advocate the use of both medical and surgical treatment". Indeed, I am happy to notice that we fully agree on endometriosis management, because also our group advocates the use of both medical and surgical treatment. In our view, the main aim of clinical research on treatment options for deep endometriosis is providing reliable data in order to allow patients to take decisions based on their preferences and priorities. They should decide, not us, because women will live with the consequences of surgical complications or with the side effects of prolonged medical treatments. The authors now specify that the women included in their cohort were resistant to medical treatment, but it is unclear what "resistant to medical treatment" really means in terms of type of medications used (analgesics only? hormonal therapies?) and for how long. Medical therapies control endometriosis but do not cure it, and several experts interpret symptoms' reappearance at drug discontinuation as a demonstration that pharmacological treatments do not work. This is conceptually wrong, and the example of severe gastro-oesophageal reflux, which could be similarly treated with medical therapy (proton pump inhibitors) or with surgery, seems to fit well here (Maret-Ouda J, Wahlin K, El-Serag HB, Lagergren J. Association Between Laparoscopic Antireflux Surgery and Recurrence of Gastroesophageal Reflux. JAMA. 2017;318:939-946. Spechler SJ. The Durability of Antireflux Surgery. JAMA. 2017;318:913-915. Garg SK, Gurusamy KS. Laparoscopic fundoplication surgery versus medical management for gastro-oesophageal reflux disease (GORD) in adults. Cochrane Database Syst Rev. 2015 Nov 5;(11):CD003243). The issue here is simply, but very importantly, to convey a fair information to patients with rectovaginal endometriosis. They have the right to make informed choices. My impression is that too vague information is provided in this report on medical treatment both before and after surgery.

	I understand (and accept) that the dataset on which this report is based does not allow to add more data in this regard, but this should have been highlighted in the Discussion section because medical treatment indeed impacts on patient reported outcomes. In particular, regarding postoperative medical therapy and its potential effect on the outcomes of surgery, the authors state in their response "Data to support the notion that long-term 'medical therapy' reduces symptoms and lesion recurrence is lacking", and "we did not present data for use of hormonal treatments as relatively few women were taking hormones post-laparoscopic surgical treatment". Please find below some text copied from the recent full NICE guideline on diagnosis and management of endometriosis. 11.3.10 Evidence to recommendations 11.3.10.1 Relative value placed on the outcomes considered The Committee prioritised pain relief, health related quality of life and adverse events as critical outcomes for their decision making and number of women requiring more surgery, absence from work and other activities of daily living and fertility as important outcomes. However, when the outcomes for the NMA were discussed subsequently, it was decided that adverse events causing withdrawal from the study and fertility would be more appropriately considered as outcomes in the NMA. 11.3.10.2 Consideration of clinical benefits and harms In view of the high rate of recurrence of endometriosis, affecting long-term quality of life for many women, improvement in long-term control of the condition was felt by the Committee to be clinically very important. The Committee were aware of the high rate of reoperation for endometriosis with associated risks of surgery and, as there was strong evidence to support this, considered that avoidance of repeat surgery by the use of long -term medical therapy would be beneficial. The Committee noted that the duration of follow-up in most studies was insufficient, but brought additional clinical experience to the discussion. Based on the evidence, the beneficial effect of all hormonal therapies was similar (probably because all work through similar mechanisms) and so the Committee considered the adverse effects of the various treatments in making their recommendation, as there are known side effects with hormonal treatments that some women may wish to avoid. In general, the Committee considered that the combined oral contraceptive pill or long-acting reversible progestogen contraceptives were the most acceptable treatments. The Committee noted that these would not be appropriate for women who were trying to conceive, although they could be used by women who were planning pregnancy at some time in the future. They also felt it was important to note that GnRHa are only licensed for 6 months due to a loss of bone density. 11.3.10.3 Consideration of economic benefits and harms The Committee discussed how the addition of hormonal treatments either before or after surgery was likely to carry a very low direct cost to the NHS and therefore could be recommended if the clinical evidence was thought strong enough to support such a recommendation. Many studies identified in the literature review used a more expensive hormonal treatment such as GnRHa in their pre / post-surgical dosage, and the economic evidence for this is more equivocal – although the model suggests that it would be cost-effective to offer such treatment at £20,000 / QALY, the Committee were told that cheaper hormonal treatments like the combined oral contraceptive pill were likely to be more cost-effective The above holds true for fertility treatments too.

	If fertility outcomes are improved by adding a hormonal treatment then this could be considered as it is likely to be cost-effective, but the Committee thought in this instance that the clinical evidence did not support offering a hormonal treatment to women attempting to become pregnant. The likely resource impact of these recommendations is somewhere between low and negative – most women who are able to tolerate hormonal treatments already receive these for endometriosis, so the Committee's recommendations were not a significant departure from current practice. Even if they were, the cost of long-acting reversible contraception is not substantial. The recommendations may cause a small cost saving, since Committee opinion is that some clinicians prescribe more expensive hormonal treatments such as GnRHas before trialling combined oral contraceptive pill or long-acting reversible progestogen contraceptives. These recommendations should prevent that unwarranted clinical variation, saving NHS resources. 11.3.10.6 Key conclusions The Committee based their recommendations on the findings of the NMA, which demonstrated that adding hormonal treatment following surgery (laparoscopic excision or ablation) reduces the risk of recurrence and symptoms, so it should be offered to women post-surgery unless they want to conceive. 11.3.11 Recommendations 46. After laparoscopic excision or ablation of endometriosis, consider hormonal treatment (with, for example, the combined oral contraceptive pill)c, to prolong the benefits of surgery and manage symptoms. In conclusion, I understand and accept that the data on which this report is based are not sufficiently detailed to define several important aspects of care that would be important for the management of women with rectovaginal endometriosis. I think it would have been important to esplicitly address this drawback and expand on the potential implication of it in the manuscript. They should have also explained in the manuscript the reason for not quantifying the dispersion of data around point estimates. Based on their reponse, the authors have chosen not to do it. Still, the merits of this study tip the balance toward publication. The endometriosis community and women with severe disease will benefit from this evidence. This report will likely become a citation classic.

REVIEWER	Charles E. Miller, MD FACOG The Advanced Gynecologic Surgery Institute, Charles E. Miller, MD & Associates, Naperville, IL United States
REVIEW RETURNED	09-Oct-2017

GENERAL COMMENTS	I think this study was a tremendous undertaking and the authors must be congratulated, not only for the study itself, but for an excellent, detailed and well-written manuscript as well. I appreciate the diligence of the other reviewers and the responses that the authors gave to us. While I do recommend acceptance of the manuscript, in my own mind, I cannot dismiss the potential impact on the study of hysterectomy and post-operative hormonal treatment. I would love to see a subsequent study that removes the hysterectomy and looks at medical treatment post-surgery for deep infiltrating endometriosis. Once again, I salute everyone involved.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Paolo Vercellini
Institution and Country: Department of Clinical Sciences and Community Health and Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Milano, Italy
Competing Interests: Disclosure of intellectual competing interest - I have a different vision on rectovaginal endometriosis management with respect to that of the authors. I am in favour of long-term medical management, and believe that surgery should be reserved for symptomatic patients who do not respond, do not tolerate, or refuse progestins, for those who have contraindications to progestins or who seek a natural conception, and those who have subocclusive bowel lesions or ureteral stenosis causing hydroureteronephrosis.

In their Response to Reviewers the authors have addressed my comments, but modifications included in the manuscript are very limited.
They maintain "Indeed, we proposed this reviewer because he had published a systematic review of medical treatments for rectovaginal endometriosis", and "It is therefore surprising that this reviewer holds such a prejudice in favour of medical treatment for the most severe form of endometriotic disease". It is not a prejudice, it is the result of decades of clinical research and experience of our centre. We would have not insisted on this aspect of management had we not observed satisfactory results with hormonal therapies.

Several reports have been published after our review confirming the effectiveness of medical treatment for deep endometriosis, including rectovaginal, bowel, and bladder forms. As a consequence, if I were a co-author of this paper, I would have avoided any comment on the purported inefficacy of hormonal treatments for rectovaginal endometriosis, also because the data provided do not allow any meaningful additional conclusion on this point (see page 5, "there is limited evidence supporting the sustained effectiveness and acceptability of medical therapies in improving the symptoms of rectovaginal endometriosis"; page 16, "its resistance to conventional medical treatments"; page 21, "in the absence of safe and effective medical therapy").
The authors state "In contrast to this reviewer, in the absence of compelling evidence to support a particular management approach, we advocate the use of both medical and surgical treatment". Indeed, I am happy to notice that we fully agree on endometriosis management, because also our group advocates the use of both medical and surgical treatment. In our view, the main aim of clinical research on treatment options for deep endometriosis is providing reliable data in order to allow patients to take decisions based on their preferences and priorities. They should decide, not us, because women will live with the consequences of surgical complications or with the side effects of prolonged medical treatments.

The authors now specify that the women included in their cohort were resistant to medical treatment, but it is unclear what "resistant to medical treatment" really means in terms of type of medications used (analgesics only? hormonal therapies?) and for how long. Medical therapies control endometriosis but do not cure it, and several experts interpret symptoms' reappearance at drug discontinuation as a demonstration that pharmacological treatments do not work. This is conceptually wrong, and the example of severe gastro-oesophageal reflux, which could be similarly treated with medical therapy (proton pump inhibitors) or with surgery, seems to fit well here (Maret-Ouda J, Wahlin K, El-Serag HB, Lagergren J. Association Between Laparoscopic Antireflux Surgery and Recurrence of Gastroesophageal Reflux. JAMA. 2017;318:939-946. Spechler SJ. The Durability of Antireflux Surgery. JAMA. 2017;318:913-915. Garg SK, Gurusamy KS.

Laparoscopic fundoplication surgery versus medical management for gastro-oesophageal reflux disease (GORD) in adults. Cochrane Database Syst Rev. 2015 Nov 5;(11):CD003243).
The issue here is simply, but very importantly, to convey a fair information to patients with rectovaginal endometriosis. They have the right to make informed choices. My impression is that too vague information is provided in this report on medical treatment both before and after surgery. I understand (and accept) that the dataset on which this report is based does not allow to add more data in this regard, but this should have been highlighted in the Discussion section because medical treatment indeed impacts on patient reported outcomes. In particular, regarding postoperative medical therapy and its potential effect on the outcomes of surgery, the authors state in their response "Data to support the notion that long-term 'medical therapy' reduces symptoms and lesion recurrence is lacking", and "we did not present data for use of hormonal treatments as relatively few women were taking hormones post-laparoscopic surgical treatment". Please find below some text copied from the recent full NICE guideline on diagnosis and management of endometriosis.

11.3.10 Evidence to recommendations
11.3.10.1 Relative value placed on the outcomes considered
The Committee prioritised pain relief, health related quality of life and adverse events as critical outcomes for their decision making and number of women requiring more surgery, absence from work and other activities of daily living and fertility as important outcomes. However, when the outcomes for the NMA were discussed subsequently, it was decided that adverse events causing withdrawal from the study and fertility would be more appropriately considered as outcomes in the NMA.
11.3.10.2 Consideration of clinical benefits and harms
In view of the high rate of recurrence of endometriosis, affecting long-term quality of life for many women, improvement in long-term control of the condition was felt by the Committee to be clinically very important. The Committee were aware of the high rate of reoperation for endometriosis with associated risks of surgery and, as there was strong evidence to support this, considered that avoidance of repeat surgery by the use of long -term medical therapy would be beneficial. The Committee noted that the duration of follow-up in most studies was insufficient, but brought additional clinical experience to the discussion. Based on the evidence, the beneficial effect of all hormonal therapies was similar (probably because all work through similar mechanisms) and so the Committee considered the adverse effects of the various treatments in making their recommendation, as there are known side effects with hormonal treatments that some women may wish to avoid.
In general, the Committee considered that the combined oral contraceptive pill or long-acting reversible progestogen contraceptives were the most acceptable treatments. The Committee noted that these would not be appropriate for women who were trying to conceive, although they could be used by women who were planning pregnancy at some time in the future. They also felt it was important to note that GnRHa are only licensed for 6 months due to a loss of bone density.
11.3.10.3 Consideration of economic benefits and harms
The Committee discussed how the addition of hormonal treatments either before or after surgery was likely to carry a very low direct cost to the NHS and therefore could be recommended if the clinical evidence was thought strong enough to support such a recommendation. Many studies identified in the literature review used a more expensive hormonal treatment such as GnRHa in their pre / post-surgical dosage, and the economic evidence for this is more equivocal – although the model suggests that it would be cost-effective to offer such treatment at £20,000 / QALY, the Committee were told that cheaper hormonal treatments like the combined oral contraceptive pill were likely to be more cost-effective
The above holds true for fertility treatments too. If fertility outcomes are improved by adding a hormonal treatment then this could be considered as it is likely to be cost-effective, but the Committee thought in this instance that the clinical evidence did not support offering a hormonal treatment to women attempting to become pregnant.

The likely resource impact of these recommendations is somewhere between low and negative – most women who are able to tolerate hormonal treatments already receive these for endometriosis, so the Committee's recommendations were not a significant departure from current practice. Even if they were, the cost of long-acting reversible contraception is not substantial. The recommendations may cause a small cost saving, since Committee opinion is that some clinicians prescribe more expensive hormonal treatments such as GnRHas before trialling combined oral contraceptive pill or long-acting reversible progestogen contraceptives. These recommendations should prevent that unwarranted clinical variation, saving NHS resources.
11.3.10.6 Key conclusions
The Committee based their recommendations on the findings of the NMA, which demonstrated that adding hormonal treatment following surgery (laparoscopic excision or ablation) reduces the risk of recurrence and symptoms, so it should be offered to women post-surgery unless they want to conceive.
11.3.11 Recommendations
46. After laparoscopic excision or ablation of endometriosis, consider hormonal treatment (with, for example, the combined oral contraceptive pill)c, to prolong the benefits of surgery and manage symptoms.

In conclusion, I understand and accept that the data on which this report is based are not sufficiently detailed to define several important aspects of care that would be important for the management of women with rectovaginal endometriosis. I think it would have been important to explicitly address this drawback and expand on the potential implication of it in the manuscript. They should have also explained in the manuscript the reason for not quantifying the dispersion of data around point estimates. Based on their response, the authors have chosen not to do it. Still, the merits of this study tip the balance toward publication. The endometriosis community and women with severe disease will benefit from this evidence. This report will likely become a citation classic.

• There is no dispute that the management of endometriosis including deep infiltrative endometriosis involving the rectovaginal space and bowel should be managed in a multi-disciplinary fashion utilising both medical and /or surgical interventions as supported in the recent NICE guideline alluded to by this reviewer. However, it is clear from the medical literature and indeed from the network meta-analysis (NMA) conducted as part of the NICE guideline process, that the effectiveness of medical treatment is variable an uncertain in the longer term and can be associated with considerable morbidity. An author on this manuscript (DB) was involved with the production of the NICE guideline and can confirm that the BSGE endometriosis database data was not used in the NMA for this guideline. The selected examples of the guideline presented by this reviewer simply point out the least burdensome medical therapies that patients may choose and the most cost-effective ones to choose. They do not cast any light or have any relevance in the comparison between medical treatment and surgery. If data of sufficient strength and quality were available the committee would likely recommend that clinicians consider medical therapy instead of surgery, but no such data were found. So the reviewers belief that there are data to support medical treatment in preference to surgery is not accepted by NICE, or by ourselves. Furthermore, the NMA included studies with a range of disease severity or where the severity of disease was not recorded. This makes generalisability and interpretation of the NMA problematic for our population – rectovaginal endometriosis

• As regards why patients choose surgery, we can only postulate, as we do not have these data. However, we know that many are taking analgesics and medical therapies and we know that in the UK patients 'choose' to have surgery. In the UK patient's choices are made in concert with the clinician (which may not be the case all over the world). The patients chose to have surgery based on their current experience and their expectation of the surgery and its risk. It is very unlikely that patients who were entirely content with medical treatment for severe deep endometriosis then went on to request an operation that carries considerable risk - logic would dictate this at the very least. This is especially likely when we are describing with such enormous numbers.

• 95% confidence intervals around point estimates have been provided in the revised manuscript (see response to Editors point 3

• We agree and are grateful for the reviewer pointing out that this paper is likely to be extremely well cited given the relevant paucity of good quality data in this enigmatic and important gynaecological disease.

Reviewer: 2
Reviewer Name: Charles E. Miller, MD FACOG
Institution and Country: The Advanced Gynecologic Surgery Institute, Charles E. Miller, MD & Associates, Naperville, IL United States
Competing Interests: None declared

I think this study was a tremendous undertaking and the authors must be congratulated, not only for the study itself, but for an excellent, detailed and well-written manuscript as well.

I appreciate the diligence of the other reviewers and the responses that the authors gave to us. While I do recommend acceptance of the manuscript, in my own mind, I cannot dismiss the potential impact on the study of hysterectomy and post-operative hormonal treatment. I would love to see a subsequent study that removes the hysterectomy and looks at medical treatment post-surgery for deep infiltrating endometriosis.

Once again, I salute everyone involved.

• Thank you for your comment. We have removed women who have undergone hysterectomy as part of their surgical treatment from the denominator of cyclical symptoms in the revised manuscript (Table 1 and Supplementary table 1). This has been adjusted in Table 2 and in Supplementary table 1 along with amendments to the footers of the tables in the revised manuscript

VERSION 3 – REVIEW

REVIEWER	Paolo Vercellini Università degli Studi and Fondazione Ca' Granda - Ospedale Maggiore Policlinico, Milan, Italy Intellectual competing interest: same as for the first and second round of revision.
REVIEW RETURNED	27-Nov-2017

GENERAL COMMENTS	In this revised version most concerns, such as inclusion of women who underwent a previous hysterectomy and lack of a measure of dispersion around point estimates, have been adequately addressed. Useful comments have been added in the Discussion section and in the boxes. This will help the readers understand in more detail some study limits. I am now satisfied with this revised version and believe the manuscript is acceptable for publication in its present form.