

Identifying pre-operative Factors Associated with Non-Responders in Women Undergoing Comprehensive Surgical Treatment for Endometriosis

Vishalli Ghai BMedSci MBBS MRCOG ,  
Haider Jan BSc MBBS MRCOG ,  
Fevzi Shakir BSc MBBS MRCOG MSc , Andrew Kent MD FRCOG

PII: S1553-4650(19)30128-1  
DOI: <https://doi.org/10.1016/j.jmig.2019.03.007>  
Reference: JMIG 3770

To appear in: *The Journal of Minimally Invasive Gynecology*

Received date: 23 August 2018  
Revised date: 9 March 2019  
Accepted date: 11 March 2019

Please cite this article as: Vishalli Ghai BMedSci MBBS MRCOG , Haider Jan BSc MBBS MRCOG , Fevzi Shakir BSc MBBS MRCOG MSc , Andrew Kent MD FRCOG , Identifying pre-operative Factors Associated with Non-Responders in Women Undergoing Comprehensive Surgical Treatment for Endometriosis, *The Journal of Minimally Invasive Gynecology* (2019), doi: <https://doi.org/10.1016/j.jmig.2019.03.007>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



# Identifying pre-operative Factors Associated with Non-Responders in Women Undergoing Comprehensive Surgical Treatment for Endometriosis

**Vishalli Ghai BMedSci MBBS MRCOG, Haider Jan BSc MBBS MRCOG, Fevzi  
Shakir BSc MBBS MRCOG MSc, Andrew Kent MD FRCOG**

## Authors

**Miss Vishalli Ghai\***, Specialist Registrar, Department of Obstetrics and  
Gynaecology, Epsom & St Helier's University Hospitals NHS Trust, Dorking Road,  
United Kingdom, KT18 7EG

**Mr Haider Jan**, Consultant Gynaecologist, Department of Obstetrics and  
Gynaecology, Epsom & St Helier's University Hospitals NHS Trust, Dorking Road,  
United Kingdom, KT18 7EG

**Mr Fevzi Shakir**, Consultant Gynaecologist, Department of Obstetrics and  
Gynaecology, Royal Free University Hospital NHS Trust, Pond St, Hampstead,  
London NW3 2QG

**Mr Andrew Kent**, Consultant Gynaecologist, Department of Obstetrics and  
Gynaecology, Royal Surrey County University NHS Hospital Trust, Egerton Road,  
Guildford, GU2 7XX

**Authors have no conflict of interest to report**

**Institutional review board/Ethics committee ruled that formal ethical approval  
was not required for this study.**

Corresponding author: Miss Vishalli Ghai, email: vishalli.ghai25@gmail.com,  
telephone: 01372 735735

Running title: Retrospective cohort study identifying pre-operative factors in non-responder women undergoing surgical treatment for endometriosis.

**Precis:** There are minimal pre-operative factors that are associated with non-response for women having surgery for endometriosis. The severity of pain experienced by women with endometriosis may be used to predict their response to surgery.

**Word count:**

Abstract: 311

Main body: 2824

## Abstract

**Study Objective:** To examine whether existing quality of health outcome measures can be used to predict or have an association with non-response surgery for endometriosis.

**Design:** Retrospective cohort study

**Settings:** Single endometriosis referral centre

**Patients:** 198 women undergoing surgery for Endometriosis

**Intervention:** Patients were given validated health questionnaires including Endometriosis Health Profile 30 (EHP-30), Gastrointestinal Quality of Life Index (GIQLI), EQ5D, hospital anxiety and depression score (HADS) pre-operatively and at 12 months post full surgical excision of endometriosis. Visual analogue scales were also used measuring dyschezia, dysmenorrhoea, dyspareunia and chronic pelvic pain. Surgical management was dependent on severity of disease. Superficial disease was treated by laparoscopic peritoneal excision or laser ablation. Deep infiltrating disease involving the bowel was excised completely together with laparoscopic bowel surgery (shave, disc or segmental resection) with/without concomitant total hysterectomy and bilateral salpingo-oophorectomy.

Non-responders were defined as women that failed to demonstrate an improvement in pain scores 12 months post-operatively.

We examined pre- and post -questionnaires, visual analogue scores, and other variables such as age of onset of symptoms, type of surgery and the presence of post-operative complications comparing responder and non-responder women to identify the factors associated with non-response.

**Measurements/Results:** Of 102 women treated for superficial endometriosis, 25 (24.51%) were non-responders. No factors were associated with non-response at 12 months. Of 96 women treated for severe endometriosis involving the bowel, 10 (10.41%) were non-responders. Non -responders had significantly less pre-operative pain ( $P=0.031$ ) and feeling of control ( $P=0.015$ ) than responders. There was no association between non-responders and women that underwent a hysterectomy with bilateral salpingo-oophorectomy or those with complications. Radical bowel surgery (resection) was associated with non-responders.

**Conclusion:** There are minimal pre-operative factors that are associated with non-response for women having surgery for endometriosis. The severity of pain experienced by women with endometriosis may be used to predict their response to surgery.

## Keywords

Endometriosis; Hysterectomy; Pelvic pain

## Introduction

Endometriosis is characterised by the presence of endometrial tissue outside the uterus that induces an inflammatory response. [1] The true prevalence of endometriosis remains unknown, however it is likely to be 2-10% of the general female population. [2] It is associated with significant long-term morbidity and may result in chronic pain, subfertility, poorer quality of life, increased socio-economic burden resulting from loss of work productivity. [3-5] [6]

Management of endometriosis largely consists of analgesic medication, hormonal treatments and surgical intervention. Surgical treatments are often based on a woman's desire for fertility, symptoms experienced and the severity of endometriosis. When other therapies fail or are unsuitable, treatment such as excision of endometriosis sometimes with concomitant hysterectomy and bilateral salpingo-oophorectomy have reported success rates of up to 75%. [7] However, a minority of women will fail to improve despite surgery whilst still being subjected to the risk of complications and a period of post-operative recovery. These women remain a diagnostic and treatment challenge, quite often in despair with pain and no available management options.

There is very limited data pertaining to predictors or factors associated with non-response to endometriosis surgery. Previous trials that have examined pre- and intra-operative risk factors for endometriosis recurrence and failure of therapy. With regards to non-responders of surgical treatment, factors such as incomplete excision of endometriosis, preservation of the cervix during subtotal hysterectomy and ovarian conservation have been suggested. While, there is some evidence available further research is required in this area. [8] [9] [10] [11] [12]

The purpose of this study is to examine whether existing quality of health outcome measures can be used to predict or have an association with non-response to surgery for endometriosis.

## Materials and Methods

This is a secondary analysis of data from two trials performed at the Royal Surrey County Hospital NHS Foundation Trust between 2007 to 2014. We defined a non-responder as women whose pain scores were the same or worse than their pre-operative states at 12 months post op using the Endometriosis Health Profile-30 questionnaire (EHP-30).

Responders were defined as those women that demonstrated an improvement in post-operative scores. Any amount of improvement was considered significant as there was no evidence for the minimum amount.

## Details of trials

We used data from a single-centre prospective cohort study: laparoscopic surgery for severe recto-vaginal endometriosis compromising the bowel. [6] This study investigated the quality of life following excision of recto-vaginal endometriosis involving the bowel (American Fertility Society classification stage IV). Quality of life outcomes were assessed pre and post operatively using validated questionnaires such as EHP-30, EQ5D, Gastro-intestinal Quality of Life Index (GIQLI), Hospital anxiety and depression score (HADS). Visual analogue scores were used to measure dysmenorrhoea, dyspareunia, dyschezia and chronic pelvic pain. Assessments were performed pre-operatively and post-operatively at 12 months. Women were eligible to participate in this study if they were undergoing surgery for severe endometriosis involving the bowel. Exclusion criteria included age less than 18 years, poor understanding of the English language and those unable to complete the consent form. The trial was registered on clinicalTrials.gov (identification number NCT02471443).

Data was also used from, Carbon Dioxide-Laser versus harmonic scalpel in the treatment of pelvic pain due to endometriosis: a double-blind randomised controlled trial. This trial evaluated whether excision of endometriosis with the harmonic scalpel was superior vaporisation with the CO<sub>2</sub> laser in the treatment of minimal, mild and moderate endometriosis (American Fertility Society classification stages I-III). The primary outcome of this trial was an evaluation of pain. Visual analogue scores were used to measure chronic pelvic pain, dysmenorrhoea, dyspareunia and dyschezia. Quality of life assessments were performed using the EHP -30 and HADS. This trial was registered on ClinicalTrials.gov (Identification number: NCT02282943). Women were eligible to participate in this study if they were over 18 years with a diagnosis of minimal to moderate endometriosis (American Fertility Society classification stages I-III).

#### Surgical Intervention

Surgical management was dependent on severity of disease. Minimal to moderate disease (American Fertility Society classification stages I-III). was treated by laparoscopic peritoneal excision using an ultrasonic energy device, the Harmonic scalpel (Ethicon Endo-Surgery, J&J Medical Ltd, Cincinnati, USA) or laser ablation. Surgeries were performed by a single gynaecological team consisting of 4 surgeons specialising in endometriosis. Treatment of deep infiltrating disease involving the bowel (American Fertility Society classification stage IV) included down-regulation using GnRH analogues for 3-6 month prior to surgery. Subsequently, all endometriosis was excised together with laparoscopic bowel surgery (rectal shave, discoid excision or segmental anterior bowel resection) with/without concomitant total hysterectomy and bilateral salpingo-oophorectomy. All surgeries were performed by a single, surgical team consisting of a high-volume gynaecological and colorectal surgeon. Please refer to the methodology of both trials for further details regarding surgical interventions.

#### Assessments

We utilised validated questionnaires such as the Endometriosis Health Profile (EHP-30) questionnaire. This self-reporting questionnaire is the instrument of choice to assess health status in trials concerning endometriosis. [13] Scores range from 0 to 100 with higher scores indicating a poorer health status. The questionnaire consists of core and modular components. The core questionnaire contains a total of 30 items across five domains: pain, control and powerlessness, emotional well-being, social support and self-image. The modular questionnaire contains 23 questions across six domains: work, relationship with children, sexual intercourse, infertility, medical profession and items. The EHP-30 has proven to be a reliable and user-friendly tool.

The Gastro-intestinal Quality of Life Index (GIQLI) is a validated questionnaire comprising of 36 questions assessing digestive symptoms, emotional, social and physical status as well as effect of medication. [14] Items are scored from 0-4, with a total ranging from 0-144. Lower scores are indicative of poorer health status. The median score for healthy individuals is 126 and those suffering from bowel disease are less than 100. [15] This questionnaire was performed in women undergoing surgery for severe endometriosis involving the bowel. This enabled an assessment of bowel function pre- and post-surgery.

The EuroQol-5 (EQ-5D) is a standardised instrument used to assess quality of life outcomes for a wide range of conditions and treatments. The EQ-5D consists of a descriptive and visual analogue system. For this study, we utilised a modified version comprising of only the visual analogue system. The visual analogue score indicates overall health status and ranges from 0 (worst health) to 100 (best health) with higher scores indicating better quality of life.

The Hospital Anxiety and Depression Scale (HADS) is self-reporting instrument of 14 items used to evaluate anxiety and depression. [16] It has advantages over other instruments and has been validated for use in a general and diverse medical population. [17] [18] [19].



Patients are asked to rate the degree to which they experience symptoms over 7 days on a scale from 0 to 3. Total scores range from 0 to 21, with higher score indicating more severe symptoms. Scores of 8-10 are borderline or suggestive of depression/anxiety and  $> 10$  indicative of mood disorder.

We used visual analogue scales to assess chronic pelvic pain, dysmenorrhoea, dyspareunia and dyschezia. Scales consisted of a 10cm horizontal line and patients were asked to place a vertical mark at a point which best represented their symptoms. Increasing severity was depicted from left to right of the scale. The distance between the left margin of the scale to the marked point was measured using a standard ruler to the nearest millimetre. Higher scores indicated severity of symptoms.

### **Ethical approval**

Carbon Dioxide-Laser versus harmonic scalpel in the treatment of pelvic pain due to endometriosis: a double-blind randomised controlled trial received ethical approval. [20] The local ethics committee deemed advised that national ethical approval was not required for the prospective cohort study: laparoscopic surgery for severe recto-vaginal endometriosis compromising the bowel as it represented service evaluation.[6]

### **Statistical analysis**

Give the lack of literature in this area we based our power calculation on a study in a similar surgical pain field concerning cholecystectomy by Lambert et al. Pre-operative pain scores were 11% lower in non-responders compared to responders after a laparoscopic cholecystectomy [21] Based on this we performed a power calculation, with a 5% significance and 90% power resulting in a sample size of 18 in each group. Statistical Analysis was performed with Statistical Package for the Social Sciences (SPSS) software version 24 (IBM, Armonk, NY, USA). Continuous variables were assessed for normality using the Shapiro-Wilk test. The Mann-Whitney test was used to compare groups of data as

they were not normally distributed. A Fishers Exact test was used to compare the relationship between categorical variables. A P-value of 0.05 was considered statistically significant

## Results

A total of 198 women had surgery for endometriosis. 96 had surgery for rectovaginal endometriosis and 102 had surgery for superficial disease.

Overall, 17.85% women (35) treated for endometriosis were identified as non-responders with no improvement or worsening pains scores at 12 months using the EHP-30. Women were more likely to be non-responders if treated for superficial endometriosis compared to those with severe endometriosis (P value =0.0089).

Of 102 women treated for superficial endometriosis, almost a quarter (25, 24.51%) were non-responders. Table 1 demonstrates results from the EHP-30, GIQLI, EQ5D, HADS and visual analogue scores comparing responder and non-responder groups. No significant factors associated with non-response at 12 months were identified including the use of laser or excision (P value 0.106). In terms, of demographics there was no difference between responder and no-responders group with regards to age (P = 0.54), AFS score (P= 0.33) or stage of disease (P= 0.22) within this cohort.

Of, 96 women treated for severe endometriosis involving the bowel, 10.41% (10 women) were non-responders. The median age of first symptoms (26 years, Q1-Q3: 18-32.5 vs 24.5 years, Q1-Q3: 17-29), age of diagnosis (32 years, Q1-Q3: 28-36 vs 27.5 years, Q1-Q3: 24-32) and age of surgery (37 years, Q1-Q3: 33-42 vs 31.5 years, Q1-Q3: 26-38) were not significant factors when comparing responder and non-responder groups respectively. Table 2 demonstrates results from the EHP-30, GIQLI, EQ5D, HADS and visual analogue scores comparing responder and non-responder groups. Only two differences were demonstrated,

non-responders experienced significantly less pre-operative pain ( $P=0.031$ ) and feelings of control ( $P=0.015$ ) than responders.

We explored the relationship between non-responders in the severe endometriosis group and various surgical variables. Women were more likely to be non-responders if they had radical bowel surgery (resection) compared to conservative bowel surgery (shave or disc excision) ( $P$  value =0.027). (Table 3) Hysterectomy and bilateral salpingo-oophorectomy ( $P$  value = 0.106) or the presence of complications (intra-operative/post-operative/bowel related such as anastomotic leak and stricture) ( $P$  value = 0.22) were not associated with non-responders .

## Discussion

This is the first study to examine whether existing quality of health outcome measures can be used to predict or have an association with non-response to surgery for endometriosis. Although, this is a secondary analysis of data, we have highlighted the significant number of women that are failing to respond to surgical interventions. Such findings are infrequently reported in literature and are of importance to both patients and clinicians. We have demonstrated that pain severity may be used to predict response to surgery for endometriosis. Furthermore, this study has also suggested that existing quality of life measures are limited in their ability to predict patient outcomes to surgery. However, our findings are limited to women attending a single tertiary endometriosis centre with experience of managing complex cases of endometriosis. The cohort of women examined in this study did not include those with severe endometriosis without bowel involvement. Additionally, the pre-operative management differed between those with minimal- moderate and severe endometriosis involving the bowel, the latter group were treated with GnRH analogues prior to surgery. Assessment tools such as visual analogue scores are also limited in their ability to capture the timing, degree and impact of symptoms on the quality of life and may require further detailed evaluation. However, the patients did complete the

EHP-30 which is a validated quality of life assessment that considers sexual function related to endometriosis. Although, these women had a confirmed diagnosis of endometriosis there has been no assessment of other contributing disorders such as muscular disorders of the pelvic floor or co-existing regional pain disorders.

Overall, we demonstrated that approximately 18% women continue to experience the same or worse pain 12 months later despite surgery for endometriosis. Findings from this study indicate that the majority of existing quality of life measures are limited in their ability to predict patient outcomes to surgery. This observation may be due to our definition of a non-responder which may be insufficient, or that these measures are indeed less pertinent when predicting patient reported outcomes to surgery. However, we have shown that severity of pain may be used to identify potential non-responders to surgical interventions for endometriosis. The fact that non-responders had lower pre-operative pain scores in those with severe endometriosis involving the bowel may be useful in counselling women with such a condition. It may be advisable to avoid complex surgery if pain is low and less likely to improve.

Additionally, there were significantly more non-responders observed in the superficial endometriosis group compared to those with recto-vaginal endometriosis. Though, these women have confirmed endometriosis diagnosed, it is possible they have contributing causes for pain such as musculoskeletal pain accounting for non-response among those with superficial disease. Response may also be based on the placebo effect of surgery alone, however this is unlikely to be of significance 6 months after surgery. [22] In the group with recto-vaginal endometriosis those who had radical bowel surgery were more likely to be non-responders. There was no difference in non-responders when comparing those that hysterectomy compared to women that did not.

As gynaecologists, our current management approach fails to address the complexity of pain sensation and perception. It is important to acknowledge and recognise that women with endometriosis may have more than one co-existing regional pain disorder. Such conditions left untreated may contribute to existing or cause pelvic pain. There is an increased frequency of irritable bowel syndrome and painful bladder syndrome observed in this population of women. Factors such as viscerovisceral convergence, peripheral and central sensitisation of pain may be responsible for this observation. Therefore, it is important to diagnose and treat co-existing disorders or consider these in instances of non-response following surgery for endometriosis.

There is evidence to suggest that endometriosis causes pain via nociceptive, inflammatory and neuropathic pathways. Presently, we are unable to determine the contribution of each pathway to the pain experienced by an individual. Surgical interventions such as laparoscopic excision and hysterectomy remove noxious stimuli but fail to address inflammatory and neuropathic pathways. Furthermore, there is no clear association between the severity of pain, extent of disease, appearance and location of endometriotic deposits. [23,24] [25] Animal studies have suggested that it is the innervation of deposits that are important for pain perception rather than visual appearance. [26] Failure to address neuropathic and inflammatory pathways may be contributing factors to non-response after surgical interventions. In such women, alternative treatments such as amitriptyline, gabapentin and pentoxifylline should be considered. [27] [28]

Hysterectomy is often perceived as the definitive treatment for refractory endometriosis. However, as our findings and other studies suggest success rates of hysterectomy vary and may fail to improve symptoms such as pain. [7] [12] Contributing factors may include preservation of ovaries, subtotal hysterectomy, incomplete excision of endometriosis, acute post-operative pain and formation of post-operative adhesions. [12] [9] [10] [8] [11] [29] [30] [31] [32] [33] [34] However, in our group they had complete excision of endometriosis and no

subtotal cases. Such factors should be considered when performing a hysterectomy for endometriosis. A nerve-sparing approach is also recommended to prevent iatrogenic damage to autonomic nerve fibres and maintain bladder, bowel and sexual function.

Pain experienced by women is an interplay of physiological, psychological and social factors. Although, not demonstrated by our study, anxiety and depression have shown to increase the risk persistent pain after hysterectomy. [30] [32]. Behaviours such as pain catastrophization, pain anxiety and pain vigilance are independently related to poorer quality of life and health outcomes in women with endometriosis. Pain catastrophization may worsen pain through cognitive and emotional changes disrupting descending endogenous pain inhibitory pathways and is associated with higher pain levels. [35] [36] However, there is evidence for the use of multifaceted care models including pain management programmes, physiotherapy and psychological therapies alongside gynaecological treatments. These have been shown to improve the severity of chronic pelvic pain, functional quality of life and health care utilisation. [37]

## **Conclusion**

We have a poor understanding of pain caused by endometriosis. There are minimal pre-operative factors that are associated with non-response for women having surgery for endometriosis. The severity of pain experienced by women with endometriosis may be used to predict their response to surgery. Further research is required to establish discriminating factors and measures that can predict response and identify women most likely to benefit from surgery. A holistic approach needs to be adopted by health professionals that addresses physiological, psychological and social aspects of pain management.

## References

- 1 Kennedy S, Bergqvist A, Chapron C, et al. ESHRE guideline for the diagnosis and treatment of endometriosis. *Hum Reprod*. 2005;2698–704. Doi: 10.1093/humrep/dei135.
- 2 Eskenazi B, Warner M L. Epidemiology of endometriosis. *Obstet Gynecol Clin North Am*. 1997;24(2):235–58.
- 3 Nnoaham Kelechi E, Hummelshoj Lone, Webster Premila, et al. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. *Fertil Steril*. 2011;96(2):366–8. Doi: 10.1016/j.fertnstert.2011.05.090.
- 4 Klein S, d'Hooghe T, Meuleman C, Dirksen C, Dunselman G, Simoens S. What is the societal burden of endometriosis-associated symptoms? a prospective Belgian study. *Reprod Biomed Online*. 2014;28(1):116–24. Doi: 10.1016/j.rbmo.2013.09.020..
- 5 Simoens S, Dunselman G, Dirksen C, et al. The burden of endometriosis: costs and quality of life of women with endometriosis and treated in referral centres. *Hum Reprod*. 2012;27(5):1292–9. Doi: 10.1093/humrep/des073.
- 6 Kent A, Shakir F, Rockall T, et al. Laparoscopic Surgery for Severe Rectovaginal Endometriosis Compromising the Bowel: A Prospective Cohort Study. *J Minim Invasive Gynecol*. 2016;23(4):526–34. Doi: 10.1016/j.jmig.2015.12.006.
- 7 Brandsborg B, Dueholm M, Nikolajsen L, Kehlet H, Jensen T.S. A prospective study of risk factors for pain persisting 4 months after hysterectomy. *Clin J Pain*. 2009;25(4):263–8. Doi: 10.1097/AJP.0b013e31819655ca.
- 8 Namnoum A.B, Hickman T.N, Goodman S.B, Gehlbach D.L, Rock J.A. Incidence of symptom recurrence after hysterectomy for endometriosis. *Fertil Steril*. 1995;64(5):898–902.
- 9 Clayton R.D, Hawe J.A, Love J.C, Wilkinson N, Garry R. Recurrent pain after hysterectomy and bilateral salpingo-oophorectomy for endometriosis: evaluation of laparoscopic excision of residual endometriosis. *Br J Obstet Gynaecol*. 1999;106(7):740–4.
- 10 Fedele L, Bianchi S, Raffaelli R, Zanconato G. Comparison of transdermal estradiol and tibolone for the treatment of oophorectomized women with deep residual endometriosis. *Maturitas*. 1999;32(3):189–93.
- 11 Behera M, Vilos G.A, Hollett-Caines J, Abu-Rafea B, Ahmad R. Laparoscopic findings, histopathologic evaluation, and clinical outcomes in women with chronic pelvic pain after hysterectomy and bilateral salpingo-oophorectomy. *The Journal of Minimally Invasive Gynecology*. 2006;13(5):431–5. Doi: 10.1016/j.jmig.2006.05.007.
- 12 Yunker A, Curlin H, Banet N, Fadare O, Steege J. Does the uterine cervix become abnormally reinnervated after subtotal hysterectomy and what is the association with future trachelectomy? *J Minim Invasive Gynecol*. 2015;22(2):261–7. Doi: 10.1016/j.jmig.2014.10.010.
- 13 Khong S, Lam A, Luscombe G. Is the 30-item Endometriosis Health Profile (EHP-30) suitable as a self-report health status instrument for clinical trials? *Fertil Steril*. 2010;94(5):1928–32. Doi: 10.1016/j.fertnstert.2010.01.047.
- 14 Nieveen Van Dijkum E.J, Terwee C.B, Oosterveld P, van der Meulen J.H, Gouma D.J, De Haes J.C. Validation of the gastrointestinal quality of life index for patients with potentially operable periampullary carcinoma. *Br J Surg*. 2000;87(1):110–5. Doi: 10.1046/j.1365-2168.2000.01307.x.
- 15 Roman H, Ness J, Suci N, et al. Are digestive symptoms in women presenting with pelvic endometriosis specific to lesion localizations? A preliminary prospective study. *Hum Reprod*. 2012;27(12):3440–9. Doi: 10.1093/humrep/des322.
- 16 Zigmond A.S, Snaith R.P. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361–70.

- 17 Moorey S, Greer S, Watson M, et al. The factor structure and factor stability of the hospital anxiety and depression scale in patients with cancer. *Br J Psychiatry*. 1991;158:255–9.
- 18 Martin C.R, Thompson D.R. A psychometric evaluation of the Hospital Anxiety and Depression Scale in coronary care patients following acute myocardial infarction. *Psychol Health Med*. 2000;5(2):193–201. Doi: 10.1080/713690189.
- 19 Woolrich R.A, Kennedy P, Tasiemski T. A preliminary psychometric evaluation of the Hospital Anxiety and Depression Scale (HADS) in 963 people living with a spinal cord injury. *Psychol Health Med*. 2006;11(1):80–90. Doi: 10.1080/13548500500294211.
- 20 Kent A, Carpenter T, Haines P, Shakir F, Pearson C, Jan H. Excisional Surgery for Endometriosis with Harmonic Scalpel Is Superior to Treatment with the CO2 Laser; a Randomised Double-Blind Controlled Trial. *J Minim Invasive Gynecol*. 2014;21(6):S10–1. Doi: 10.1016/j.jmig.2014.08.053.
- 21 Lamberts M.P, Oudsten Den B.L, Gerritsen J.J.G.M, et al. Prospective multicentre cohort study of patient-reported outcomes after cholecystectomy for uncomplicated symptomatic cholelithiasis. *Br J Surg*. 2015;102(11):1402–9. Doi: 10.1002/bjs.9887.
- 22 Duffy J.M.N, Arambage K, Correa F.J.S, Olive D, Farquhar C, Garry R, Barlow D.H, Jacobson TZ. Laparoscopic surgery for endometriosis. Cochrane Database of Systematic Reviews 2014, Issue 4. Art.No.: CD011031. DOI: 10.1002/14651858.CD011031.pub2.
- 23 Fauconnier A, Chapron C. Endometriosis and pelvic pain: epidemiological evidence of the relationship and implications. *Hum Reprod Update*. 2005;11(6):595–606. Doi: 10.1093/humupd/dmi029.
- 24 Hsu A.L, Sinaii N, Segars J, Nieman L.K, Stratton P. Relating Pelvic Pain Location to Surgical Findings of Endometriosis. *Obstet Gynecol*. 2011;118(2, Part 1):223–30. Doi: 10.1097/AOG.0b013e318223fed0.
- 25 Menakaya U, Lu C, Infante F, Lam A, Condous G. Relating historical variables at first presentation with operative findings at laparoscopy for endometriosis. *Aust N Z J Obstet Gynaecol*. 2014;54(5):480–6. Doi: 10.1111/ajo.12256.
- 26 Berkley K.J, Dmitrieva N, Curtis K.S, Papka R.E. Innervation of ectopic endometrium in a rat model of endometriosis. *Proc Natl Acad Sci USA*. 2004;101(30):11094–8. Doi: 10.1073/pnas.0403663101.
- 27 Sator-Katzenschlager S.M, Scharbert G, Kress H.G, et al. Chronic pelvic pain treated with gabapentin and amitriptyline: a randomized controlled pilot study. *Wien Klin Wochenschr*. 2005;117(21–22):761–8. Doi: 10.1007/s00508-005-0464-2.
- 28 Kamencic H, Thiel J.A. Pentoxifylline after conservative surgery for endometriosis: a randomized, controlled trial. *The Journal of Minimally Invasive Gynecology*. 2008;15(1):62–6. Doi: 10.1016/j.jmig.2007.07.018.
- 29 Brandsborg B, Nikolajsen L, Hansen C.T, Kehlet H, Jensen T.S. Risk factors for chronic pain after hysterectomy: a nationwide questionnaire and database study. *Anesthesiology*. 2007;106(5):1003–12. Doi: 10.1097/01.anes.0000265161.39932.e8.
- 30 Pinto P.R, McIntyre T, Nogueira-Silva C, Almeida A, Araújo-Soares V. Risk factors for persistent postsurgical pain in women undergoing hysterectomy due to benign causes: a prospective predictive study. *J Pain*. 2012;13(11):1045–57. Doi: 10.1016/j.jpain.2012.07.014.
- 31 Theunissen M, Peters M.L, Schepers Jan, et al. Recovery 3 and 12 months after hysterectomy: epidemiology and predictors of chronic pain, physical functioning, and global surgical recovery. *Medicine (Baltimore)*. 2016;95(26):e3980. Doi: 10.1097/MD.0000000000003980.
- 32 Han C, Ge Z, Jiang W, Zhao H, Ma T. Incidence and risk factors of chronic pain following hysterectomy among Southern Jiangsu Chinese Women. *BMC Anesthesiol*. 2017;17(1):103. Doi: 10.1186/s12871-017-0394-3.



- 33 Sng B.L, Ching .Y, Han Nian-Lin R, et al. Incidence and association factors for the development of chronic post-hysterectomy pain at 4- and 6-month follow-up: a prospective cohort study. *J Pain Res.* 2018;11:629–36. Doi: 10.2147/JPR.S149102.
- 34 Pokkinen S.M, Nieminen K, Yli-Hankala A, Kalliomäki M. Characterization of persistent pain after hysterectomy based on gynaecological and sensory examination. *Scand J Pain.* 2016;11(1):42–8. Doi: 10.1016/j.sjpain.2015.11.011.
- 35 Sullivan M.J.L, Lynch M.E, Clark A.J. Dimensions of catastrophic thinking associated with pain experience and disability in patients with neuropathic pain conditions. *Pain.* 2005;113(3):310–5. Doi: 10.1016/j.pain.2004.11.003.
- 36 Martin C.E, Johnson E, Wechter M.E, Leserman J, Zolnoun D.A. Catastrophizing: a predictor of persistent pain among women with endometriosis at 1 year. *Hum Reprod.* 2011;26(11):3078–84. Doi: 10.1093/humrep/der292.
- 37 Allaire C, Williams C, Bodmer-Roy S, et al. Chronic pelvic pain in an interdisciplinary setting: 1-year prospective cohort. *Am J Obstet Gynecol.* 2017. Doi: 10.1016/j.ajog.2017.10.002.

ACCEPTED MANUSCRIPT

**Table 1- Demonstrating assessment resulting comparing responder and non-responders among women treated for superficial endometriosis**

| Domain  |              | Median | Q1-Q3     | P Value |
|---|--------------|--------|-----------|---------|
| <b>EHP-30 Pain score</b>                            | Non-response | 27.3   | 18.2-50   | 0.088   |
|   | Responded    | 43.2   | 29.5-54.5 |         |
| <b>EHP-30 Feeling of control score</b>              | Non-response | 50     | 29.2-58.3 | 0.192   |
|   | Responded    | 54.2   | 37.5-66.7 |         |
| <b>EHP-30 Emotional wellbeing score</b>             | Non-response | 41.7   | 29.2-45.8 | 0.102   |
|   | Responded    | 45.8   | 33.3-58.3 |         |
| <b>EHP-30 Social support score</b>                  | Non-response | 25     | 0-50      | 0.076   |
|   | Responded    | 43.8   | 18.8-62.5 |         |
| <b>EHP-30 Self-image score</b>                      | Non-response | 33.3   | 8.3-41.7  | 0.647   |
|   | Responded    | 33.3   | 8.3-50    |         |
| <b>EHP-30 Sexual relationships score</b>            | Non-response | 40     | 27.5-60   | 0.102   |
|   | Responded    | 65     | 30-80     |         |
| <b>Hospital anxiety and anxiety score (HADS)</b>    | Non-response | 8      | 6.5-9     | 0.183   |
|   | Responded    | 10     | 7-12      |         |
| <b>Hospital anxiety and depression score (HADS)</b> | Non-response | 2      | 1-4       | 0.063   |
|   | Responded    | 4      | 2-6       |         |
| <b>Visual analogue score (VAS) dysmenorrhoea</b>    | Non-response | 70     | 48.8-79   | 0.342   |
|   | Responded    | 70     | 60-80     |         |
| <b>Visual analogue score (VAS) pelvic pain</b>      | Non-response | 58.65  | 0-70      | 0.755   |
|   | Responded    | 57.1   | 36.9-75   |         |
| <b>Visual analogue score (VAS) dyspareunia</b>      | Non-response | 49.7   | 0-80      | 0.795   |
|   | Responded    | 52.2   | 15-77.1   |         |
| <b>Visual analogue score (VAS) dyschezia</b>        | Non-response | 25.6   | 0-54.2    | 0.743   |
|   | Responded    | 25.15  | 0-67.9    |         |

**Table 2- Demonstrating assessment resulting comparing responder and non-responders among women treated for severe endometriosis**

| Domain   |              | Median | Q1-Q3      | P Value |
|--|--------------|--------|------------|---------|
| <b>EHP-30 Pain score</b>                           | Non-response | 50     | 20.5-63.6  | 0.031   |
|  | Responded    | 60.25  | 47.7-72.7  |         |
| <b>EHP-30 Feeling of control score</b>             | Non-response | 62.5   | 45.8-70.8  | 0.015   |
|  | Responded    | 79.2   | 66.7-91.7  |         |
| <b>EHP-30 Emotional wellbeing score</b>            | Non-response | 62.5   | 45.8-70.8  | 0.367   |
|  | Responded    | 54.2   | 41.7-70.8  |         |
| <b>EHP-30 Social support score</b>                 | Non-response | 50.05  | 43.8-68.8  | 0.661   |
|  | Responded    | 59.4   | 37.5-81.3  |         |
| <b>EHP-30 Self-image score</b>                     | Non-response | 41.7   | 33.3-75    | 0.508   |
|  | Responded    | 50     | 25-83.3    |         |
| <b>EHP-30 Effect on work score</b>                 | Non-response | 57.5   | 45-60      | 0.86    |
|  | Responded    | 55.5   | 30-75      |         |
| <b>EHP-30 Effect on relationship with children</b> | Non-response |        |            | 0.789   |
|  | Responded    | 62.5   | 37.5-75    |         |
| <b>EHP-30 Sexual relationships score</b>           | Non-response | 35     | 25-75      | 0.208   |
|  | Responded    | 75     | 45-93.8    |         |
| <b>EHP-30 Infertility score</b>                    | Non-response | 71.9   | 68.8-90.65 | 0.27    |
|  | Responded    | 68.8   | 31.3-81.3  |         |
| <b>EHP-30 Medical professional score</b>           | Non-response | 12.55  | 3.15-43.8  | 0.88    |
|  | Responded    | 18.8   | 0-43.8     |         |
| <b>EQ 5D</b>                                       | Non-response | 55     | 48-70      | 0.673   |
|  | Responded    | 60     | 39.75-70   |         |
| <b>GIQLI</b>                                       | Non-response | 71.9   | 68.8-90.65 | 0.375   |
|  | Responded    | 83.5   | 71-100     |         |
| <b>Visual analogue</b>                             | Non-response | 70     | 22-95.5    | 0.358   |

|  |              |      |           |       |
|--|--------------|------|-----------|-------|
| <b>score (VAS) dysmenorrhoea</b>               |              |      |           |       |
|  | Responded    | 85   | 66-95     |       |
| <b>Visual analogue score (VAS) pelvic pain</b> | Non-response | 65   | 60-82     | 0.717 |
|  | Responded    | 68.5 | 42-86     |       |
| <b>Visual analogue score (VAS) dyspareunia</b> | Non-response | 67.5 | 22-84     | 0.671 |
|  | Responded    | 57   | 13.5-79.5 |       |
| <b>Visual analogue score (VAS) dyschezia</b>   | Non-response | 53   | 25.5-61.5 | 0.446 |
|  | Responded    | 66   | 24-83     |       |

**Table 3- Demonstrating bowel surgery among responders and non-responders in the severe endometriosis group**

| <b>Type of Bowel Surgery</b>          | <b>Number of responders</b> | <b>Number of non-responders</b> | <b>Total</b> |
|---------------------------------------|-----------------------------|---------------------------------|--------------|
| Conservative (shave or disc excision) | 37                          | 1                               | 38           |
| Radical bowel surgery (resection)     | 42                          | 9                               | 51           |
| Total                                 | 79                          | 10                              | 89           |