

BMJ Open Robotic versus laparoscopic surgery for severe deep endometriosis: protocol for a randomised controlled trial (ROBEndo trial)

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ABSTRACT

Introduction Endometriosis is a common gynaecological disease affecting around 10% of fertile-aged women, causing severe pain symptoms. Deep endometriosis is defined as endometriotic implants that infiltrate the underlying organs more than 5 mm in depth. Surgery for deep endometriosis requires advanced multidisciplinary surgical technique, often in very difficult surgical conditions, with increased risks of complications. Robotic surgery offers a high-definition three-dimensional view and articulating instruments that may allow more precise dissection than conventional laparoscopy in the pelvic area. The superiority of robotic surgery has not, however, been proved in randomised controlled studies, and there is a lack of long-term outcome data. Advanced endometriosis surgery offers an excellent platform to study the feasibility and long-term outcomes of robotic surgery compared with conventional laparoscopy.

Methods and analysis ROBEndo is a prospective, randomised, controlled clinical trial in a single-centre setting. Patients with deep endometriosis verified by MRI needing surgery at Oulu University Hospital (Oulu, Finland) will be considered eligible. 70 patients will be allocated 1:1 to receive either robotic-assisted or conventional laparoscopic surgery in two strata: radical surgery (with the removal of the uterus and adnexae) and gynaecological organ-sparing surgery. The primary outcome will be the surgical outcome as regards to pain symptoms measured on numeric rating scale (NRS) questionnaires at 24 hours and 6, 12 and 24 months postoperatively. As secondary outcomes, intraoperative measures, enhanced recovery after surgery factors, complications, cost and long-term quality of life measured with Endometriosis Health Profile-30 (EHP-30), Female Sexual Function Index (FSFI) and 15-dimensional (15D) questionnaires will be compared.

Ethics and dissemination This study has been approved by the Northern Ostrobothnian Hospital District Ethical Committee at Oulu University Hospital (212/2021). Informed consent will be obtained during the preoperative check-up by the operating gynaecologist. The results will be published in peer-reviewed international journals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This trial compares robotic deep endometriosis surgery with conventional laparoscopy in a randomised, controlled setting, focusing on outcomes related to longer-term pain relief and quality of life.
- ⇒ SPIRIT checklist guidelines were followed when drafting this study protocol.
- ⇒ The relatively small sample size may be considered a limitation to this study, although the sample size was based on a power calculation.
- ⇒ The trial is taking place in a single tertiary referral hospital with specific experience in advanced endometriosis surgery, so caution should be exercised with respect to generalising the results.

Trial registration number NCT05179109.

INTRODUCTION

Background and rationale

Endometriosis is a common gynaecological disease affecting around 10% of the fertile-aged female population. For unknown reasons, endometrium-like cells are implanted outside the uterus, mainly in the abdominal cavity, responding to menstrual cycle with bleeding, thus causing pain. At worst, endometriosis is a chronic disease that causes severe pain symptoms from teenage years to menopause, impairing the quality of life and also fecundity markedly.¹ Deep endometriosis is defined as endometriotic implants that infiltrate the underlying organs more than 5 mm in depth. Most commonly these implants are located in the pelvic area, namely in bowel, rectovaginal septum, urinary organs and sacrouterine ligaments. Endometriosis induces abdominal cavity inflammation that predisposes to severe adhesion formation between gynaecological and surrounding organs.

The main goal of endometriosis surgery is symptom relief by restoring organ anatomy and function with total excision of endometriotic tissue, keeping in mind that endometriosis is a benign condition and hence no unreasonable postoperative harm for the patient is accepted. Therefore, endometriosis surgery requires advanced surgical techniques with deep, but tissue-sparing, pelvic dissection, often in very difficult surgical conditions with increased risks of complications. A multidisciplinary team including gynaecologists, colorectal surgeons and urologists is also frequently required, creating a need for centralisation of endometriosis surgery to centres with sufficient competence and instrumentation.

In the past decade, robotic surgery has gained popularity in benign operative gynaecology. It has been suggested that endometriosis surgery is suitable, if not most suited, for robotic assistance due to the technically challenging operative circumstances.² Robotic assistance offers a high-definition three-dimensional view and articulating instruments that may allow more precise dissection than conventional laparoscopy in the pelvic area. This has not, however, been sufficiently proved in randomised controlled studies.³ As expected, robotic surgery has been shown to offer certain benefits in patient recovery in comparison to laparotomy, such as lower postoperative pain and morbidity as well as shorter hospital stay.² Also, same-day discharge after robotic-assisted hysterectomy has been found feasible and safe.⁴

Proving benefits in comparison to laparoscopy, which is the gold standard of endometriosis surgery is, however, more difficult due to the already minimally invasive nature of laparoscopy. There is obvious lack of data in this respect. We were able to find five controlled studies comparing robotics with traditional laparoscopy in endometriosis surgery,^{5–9} but only one with a randomised study plan.¹⁰ Most studies, except the randomised controlled trial (RCT) by Soto *et al*,¹⁰ showed an increased operating time in the robotic group with no other significant differences in the intraoperative or postoperative outcomes.^{5–7,9} Only one study had a postoperative quality of life follow-up up to 6 months with no significant differences between robotic and laparoscopic surgery.¹⁰ A non-inferiority of robotic surgery in comparison to laparoscopic endometriosis surgery has been stated,¹¹ but not superiority.¹²

Robotic surgery is an intriguing addition to current surgical approaches in gynaecology. It may offer certain patient and work-ergonomic-related benefits, the high procedure-related costs being a demerit. Therefore, and in order to be able to choose the most suitable patients for robotic surgery, it is of importance to investigate the role of robotic gynaecologic surgery in a randomised, controlled setting. In our opinion, endometriosis surgery offers an excellent platform for this research. Furthermore, the most important outcomes of endometriosis surgery, namely long-term symptom relief, improved fertility and enhanced quality of life, can only be studied in longer-term follow-up studies that are lacking to date.

Objectives

The objective of this study is to examine whether robot-assisted laparoscopy is superior compared with conventional laparoscopy as regard to patient outcome immediately after surgery, as well as at 6, 12 and 24 months postoperatively, measured by questionnaires concerning the pain symptoms and disease-related quality-of life.

METHODS AND ANALYSIS

Study design and setting

The ROBEndo trial is a prospective, randomised, controlled clinical trial with an allocation ratio of 1:1. The trial is a single-centre study being conducted at a tertiary university hospital in Finland.

Eligibility criteria

Inclusion criteria

1. Age 18–50.
2. ASA (American Society of Anaesthesiologists physical status classification) 1–3.
3. Diagnosed deep endometriosis (MRI).
4. Patient has symptoms.
5. Operative treatment is indicated.
6. Patient is able to give informed consent.

Exclusion criteria

1. ASA >3.
2. Recurring rectosigmoid endometriosis.

Interventions

Intervention description

The extent of the surgery will be based on the clinical condition of the patient and the stage of endometriosis. The surgical intervention will be performed either by robotic assistance or conventional laparoscopy according to allocation. In addition, block randomisation will be used, depending on whether radical surgery with the removal of the uterus and adnexae or gynaecological organ-sparing surgery will be performed. All anaesthesia measures will be standardised.

Modifications

Trial participants have the right to withdraw from the study at any time, should they wish to do so, without any consequences. Any other causes to discontinue or modify allocated interventions are not probable.

Adherence

Trial participants will be given their scheduled follow-up appointments at hospital discharge. A reminder text-message will be sent prior to the appointment to each participant in order to improve adherence.

Concomitant care

Treatment of the patient will be conducted by standard care protocol regardless of the trial participation. The postoperative care follows enhanced recovery after surgery (ERAS) protocol used in the clinic.

Outcomes

Primary outcome

The surgical outcome as regard to pain symptoms (NRS (numeric rating scale) questionnaire) immediately postoperatively (24 hours) and 6, 12 and 24 months postoperatively, described as absolute NRS scores and change from baseline for both study groups.

Secondary outcomes

1. Intraoperative measures: Operation time (minutes), blood loss (mL), complications (classified according to Clavien-Dindo) for both study groups.
2. Factors concerning ERAS: nausea (yes/no), vomiting (yes/no), peroral intake (minutes from surgery), mobilisation (minutes from surgery), bowel movement (minutes from surgery), time of discharge (hours after surgery), complications (classified according to Clavien-Dindo) for both study groups.
3. Cost, euros, primary hospital stay and 24 months, for both study groups.
4. Complications (classified according to Clavien-Dindo), readmissions to hospital within 30 days.
5. Endometriosis-related quality-of-life (Endometriosis Health Profile-30 (EHP-30)) at 6, 12 and 24 months, described as absolute scores and change from baseline for both study groups.
6. General quality-of-life (15-dimensional questionnaire (15D)) at 6, 12 and 24 months, described as absolute scores and change from baseline for both study groups.
7. Sexual quality-of-life (Female Sexual Function Index (FSFI)) at 6, 12 and 24 months, described as absolute scores and change from baseline for both study groups.

Participant timeline

The participant timeline for the study is shown in [table 1](#).

Sample size

Sample size was estimated assuming a 2.5 (SD 3.0) between group difference in pain (NRS scale) at 12 months postoperatively.¹³ By using $\alpha=0.05$, 10% drop-out rate and assuming a conservative zero correlation between repeated measurements, we need to randomise 35 patients per group to achieve 90% statistical power.

Recruitment

All eligible patients referred to gynaecological outpatient clinic at Oulu University Hospital with diagnosed deep endometriosis needing surgical treatment will be considered as potential trial participants. The diagnosis of deep endometriosis is based on MRI. After receiving thorough information on the study protocol including possible advantages and disadvantages, and after voluntary signing of the informed consent, the trial participants will be enrolled.

Allocation

The allocation sequence will be generated using a computer-generated random number list. Study group will be marked in opaque envelopes that will be drawn correspondingly to the random numbers list. The patient will be blinded to the allocation, which will be performed in two strata: radical surgery (with the removal of the uterus and adnexae) and gynaecological organ-sparing surgery. A separate allocation list will be produced for both strata. We use randomly varying block size (2, 4 and 6) within strata.

Table 1 Participant timeline

Timepoint	Enrolment	Allocation	OR	Postoperative	6 months	12 months	Close-out 24 months
Visit no	1	2	3		4	5	6
Enrolment							
Eligibility screen	x						
Informed consent	x						
Allocation		x					
Interventions							
Robotic surgery			x				
Laparoscopic surgery			x				
Assessments							
Clinical investigation	x				x	x	x
Endometriosis classification Enzian			x				
Recovery measures				x			
Pain (NRS)	x			x	x	x	x
Disease-specific quality of life (EHP-30)	x				x	x	x
General quality of life (15D)	x				x	x	x
Sexual quality of life (FSFI)	x				x	x	x

15D, 15-dimensional questionnaire; EHP-30, Endometriosis Health profile; FSFI, Female Sexual Function Index; NRS, Numeric rating scale.

The allocation sequence will be concealed by using sealed envelopes. The envelopes will be opened after the preoperative visit to the outpatient clinic in order to schedule the OR specifics.

The assignment of participants to interventions will be performed by the outpatient clinic nurse. The nurse will not participate in the treatment of the patient afterwards. The enrollment will be performed by the surgeons at the presurgery visit at the outpatient clinic.

Blinding (masking)

Blinding mechanism

The trial participants will be blinded to interventions; that is, they will not be informed of the surgical method per se.

Emergency unblinding

Emergency unblinding is not likely to be needed in this study.

Data collection

Trial procedures and evaluations

Data will be collected prospectively on an electronic SPSS (Version 27) sheet designed for this study. Validated questionnaires (NRS, EHP-30, 15D, FSFI) will be used at the baseline and for collecting outcome data concerning postoperative results as regard to pain and quality-of-life at 6, 12 and 24 months postoperatively.

Retention

Any trial participant lost to follow-up will be contacted in order to complete the 24-month follow-up. Participant withdrawal during the postoperative hospital stay is not likely.

Data management

All data will be handled with utmost care and confidentiality. Data will be saved electronically with passwords and any manual data will be stored behind locked doors at the clinic. Data entry is possible only for the authoring investigators.

Statistical methods

Outcomes

We will report mean with SD or median with 25th–75th percentiles for continuous variables and frequencies with percentages for categorical variables. Cross-sectional data will be analysed using Student's t-test or Welch test (continuous data) and Fisher's exact test (categorical data). Repeatedly measured continuous data will be analysed using linear mixed model (LMM). In LMM, we use patient as random effect and treatment, time, the interaction of treatment and time as fixed factors, and the stratification factor of radical surgery or gynaecological organ-sparing surgery will be set as a covariate. Effect sizes with 95% CIs will be reported according to LMM.

Additional analyses

A separate subgroup analysis within both strata will be performed. However, as the power calculation is

performed only for primary outcome, the secondary outcomes and subgroup analyses are considered as supportive, exploratory and/or hypothesis generating.

Analysis population and missing data

The analyses will be performed on an intention-to-treat basis, that is, all randomised participants will be analysed in the group which they were originally allocated. Per-protocol analysis will be performed as sensitivity analysis. If there are missing data on the primary outcome, a multiple imputation method will be used.

Data monitoring

Formal committee

No data monitoring committee is planned for this single-centre researcher-driven study.

Interim analysis

No interim analyses are planned.

Safety/harms

Possible adverse events and other unintended effects of the trial will be documented on trial data and medical records. All significant adverse events will be listed specifically. Patients are covered by the Finnish Patient Insurance Centre.

Auditing

No external auditing is planned for this single-centre study.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

ETHICS AND DISSEMINATION

Research ethics approval

The ROBEndo trial study plan has been approved by the Northern Ostrobothnian Hospital District Ethical Committee at Oulu University Hospital (212/2021).

Protocol amendments

In case of possible future protocol modifications, The Ethical Committee at Oulu University Hospital will be informed.

Informed consent process

Informed consent will be obtained during the preoperative check-up at the outpatient clinic by the operating gynaecologist/informed consent material (in Finnish language) has been approved by the Northern Ostrobothnian Hospital District Ethical Committee (online supplemental files 1 and 2).

Confidentiality

Patient identity will be secured by using anonymous id-codes generated for this study instead of personal social security PIN-codes. Any data management will be

performed by id-codes throughout the study period and after the trial.

Access to data

Due to Finnish laws on privacy protection the raw data from the study are not available for public use. However, on reasonable request, statistical code and data output may be available from the corresponding author.

Ancillary and post-trial care

Ancillary and post-trial care including the care of possible complications will be given according to standard medical practice irrespectively to the trial itself. Complications caused by interventions given within the trial are compensated via the Finnish Patient Insurance Centre.

Dissemination policy

The trial results will be published in peer-reviewed international journals focusing on the investigatory field in question. Results at 12 and 24 months, as well as cost analysis at 24 months will be published separately. Trial participants will not be informed on the results.

DISCUSSION

Since the Food and Drug Administration (FDA) approval in 2005, robotic surgery has been widely accepted and used in the treatment of a variety of surgical conditions. Robot-assisted surgery was introduced to overcome the drawbacks of open and laparoscopic surgery, and to improve surgical performance. The main advantages of robotic surgery are better ergonomics, enhanced dexterity due to articulated instruments, tremor filtration and a three-dimensional optical system with a better depth perception.^{14 15} The main limitations include lack of tactile feedback and high costs compared with other surgical methods.¹⁵ During the last decade robotic assistance has become more popular also in endometriosis surgery, but to date, there is insufficient RCT data to support the use of robotics.

Conventional laparoscopic surgery has been the gold-standard treatment in endometriosis when conservative treatment fails.¹⁶ Endometriosis surgery aims to symptom relief, improved fecundity and above all to an improved quality of life by removing all visible endometriotic foci. Endometriosis surgery with an advanced stage of disease is challenging requiring an experienced multidisciplinary team of experts. Robotics serves a flexible platform for multidisciplinary approach with advantages in deep and precise dissection in female pelvis, that may allow a more radical excision of the disease and a better long-term outcome for the patient. Previous literature, that is scarce, has been focusing on the perioperative and short-term postoperative outcome after robotic endometriosis surgery and the long-term quality of life results are lacking.

To fill in that data, we prepared this protocol for a trial that will be one of the first trials investigating both

short-term perioperative and postoperative outcomes as well as long-term quality of life outcomes up to 2 years after surgery in a randomised, controlled setting. Our sample size is relatively small, which could be considered a limitation. However, a power calculation based on previous literature was performed and serves as a basis for the chosen sample size. This trial is being conducted at a single tertiary referral hospital with specific experience in advanced endometriosis surgery, and therefore caution should be exercised when generalising the results. Increased knowledge on the possibilities of gynaecological robotic surgery may help medical professionals in decision making concerning patient selection as well as resource and cost management.

Contributors AMT is the first author. She contributed to the conception of the study design, and contributed to surgery of the study subjects, data collection and interpretation as well as the preparation of the manuscript. SK is the principal investigator, contributed to conception of the study design, and contributed to surgery, data collection and interpretation, as well as the preparation of the manuscript. TR and JM-K contributed to the conception of the study design, and contribute to surgery, data collection and interpretation, as well as the preparation of the manuscript. PO is the lead methodologist, contributed to the conception of the study design, is responsible of data analysis and contributes to the preparing of the manuscript. TP and OU contributed to conception of the study design and preparing of the manuscript. All authors will read and approve the final manuscript.

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Competing interests None declared.

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