The cost-effectiveness of surgical excision of colorectal endometriosis compared to ART treatment trajectory (TOSCA study) in the management of colorectal endometriosis and subfertility

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Reproduction & Fertility

Reproduction and Fertility (2024) **5** e230048
https://doi.org/10.1530/RAF-23-0048

Received 13 July 2023
Accepted 5 April 2024
Available online 5 April 2024
Version of Record published 30 April 2024

PROTOCOL

The cost-effectiveness of surgical excision of colorectal endometriosis compared to ART treatment trajectory (TOSCA study) in the management of colorectal endometriosis and subfertility

Study protocol for a multicentre prospective patient preference trial in the Netherlands

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Abstract

Currently, the optimal treatment to increase the chance of pregnancy and live births in patients with colorectal endometriosis and subfertility is unknown. Evidence suggests that that both surgery and *in vitro* fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) are effective in improving the live birth rate (LBR) among these women. However, the available evidence is of low quality, reports highly heterogeneous results, lacks direct comparison between both treatment options, and does not assess whether a combination strategy results in a higher LBR compared to IVF/ICSI-only treatment. Additionally, the optimal timing of surgery within the treatment trajectory remains unclear. The primary objective of the TOSCA study is to assess the effectiveness of surgical treatment (potentially combined with IVF/ICSI) compared to IVF-/ICSI-only treatment to increase the chance of an ongoing pregnancy resulting in a live birth in patients with colorectal endometriosis and subfertility, measured by cumulative LBR. Secondary objectives are to assess and compare quality of life and cost-effectiveness in both groups. Patients will be followed for 40 months after inclusion or until live birth. The TOSCA study is expected to be completed in 6 years.

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Reproduction and Fertility (2024) **5** e230048
https://doi.org/10.1530/RAF-23-0048

Trial registration number: The TOSCA trial is registered as 'Cost-Effectiveness of Surgical Excision of Colorectal Endometriosis Compared to ART Treatment Trajectory (TOSCA)' in the Clinical Trials Register (NCT No. NCT05677269, https://clinicaltrials.gov/ct2/show/NCT05677269)

Date of first patient enrolment: The first patient was included in February 2023.

Lay summary

Treating bowel endometriosis in people with fertility problems is difficult, and at the moment, there is no consensus on the best way to increase the chances of pregnancy. This makes it hard for gynaecologists to advise people when to have either IVF/ICSI or surgery, particularly in patients with fewer pain symptoms, as the benefits of surgery to enhance fertility have to be balanced against the potential risk of side effects. Surgery can improve fertility and pain symptoms, but it may delay people trying to conceive which means the reserve of eggs in the ovaries will reduce with time. IVF/ICSI also seems a viable option, but having the surgery first may increase the chances of conception (both naturally and/or after IVF/ICSI). The TOSCA study aims to determine whether surgery for bowel endometriosis leads to an increased birth rate and better patient reported outcome measures compared to IVF/ICSI alone.

Keywords: ART; assisted reproduction; colorectal endometriosis; cost-effectiveness; fertility-enhancing surgery; live birth; pregnancy

Introduction

Endometriosis is estimated to affect 10% of reproductive-age females (Zondervan *et al.* 2020). It is characterised by the presence of extra-uterine endometrium-like tissue, inducing chronic inflammation and adhesion formation. Two clinical hallmarks commonly associated with endometriosis are subfertility, with up to 50% of subfertile women being affected by the condition, and severe pain including dysmenorrhoea, dyschezia, dysuria, dyspareunia and chronic pelvic pain (Meuleman *et al.* 2009, Zondervan *et al.* 2020). As a result, women with endometriosis experience a significant reduction in their quality of life, social participation, sexual intimacy, mental health and work productivity (Nnoaham *et al.* 2011, Chen *et al.* 2016, Zondervan *et al.* 2020). Consequently, the economic burden associated with this condition is significant, estimated at €9579 per women annually. The majority of this burden is attributed to productivity loss (66%), followed by healthcare costs (33%) (Simoens *et al.* 2012). In the United States, the economic burden per endometriosis patients ($9754–14,881 per patient) has been calculated to be even higher compared to the costs per diabetes patient ($8767 per patient). Despite this high financial burden, there remains a lack of sufficient funding and attention dedicated to endometriosis (Ellis *et al.* 2022).

Among all anatomical locations where endometriosis can manifest, the bowel is affected in 5–12% of women with endometriosis (#Enzian C1, C2, C3, FI), with involvement of the colorectum in 90% of cases (Keckstein *et al.* 2021, Becker *et al.* 2022). While the sole impact of colorectal endometriosis on fertility remains inconclusive, as other intraperitoneal endometriosis lesions are frequently present, it is likely that fertility is affected by multiple mechanisms (Chapron *et al.* 2003). These mechanisms include inflammatory alterations in peritoneal fluid, alterations in oestrogen and progesterone hormone levels, lowered endometrium receptivity, associated adenomyosis, a diminished ovarian reserve (in the case of endometriomas or prior ovarian surgery) and adhesion formation that disrupts adnexal anatomy and function (Zondervan *et al.* 2020, Maignien *et al.* 2021). Furthermore, dyspareunia and/or chronic pelvic pain may impede (timed) intercourse. The management of colorectal endometriosis and subfertility is challenging, and at the moment, there is no consensus on the optimal treatment strategy to increase the chance of conceiving. Therefore, the primary aim of this study is to identify the optimal treatment for women with colorectal endometriosis and subfertility to increase the chance of an ongoing pregnancy resulting in a live birth.

The two treatment approaches available to increase the chance of conceiving in subfertile women with colorectal endometriosis are artificial reproductive technology (ART), including *in vitro* fertilisation (IVF)/intracytoplasmic sperm injection (ICSI), and complete laparoscopic excision of (colorectal) endometriosis lesions. The latter is usually preferred in cases where the patient experiences severe pain (Iversen *et al.* 2017). Three surgical techniques are used to resect colorectal endometriosis, depending on the size and extent of infiltration of the lesion: bowel shaving, disc resection and segmental resection (Barra *et al.* 2021). Evidence shows that surgery can significantly improve the quality of life (QoL) and reduce pain symptoms (Riiskjær *et al.* 2018, Becker *et al.* 2022). Additionally, it indicates that surgery may positively impact the likelihood of conceiving (naturally and/or after IVF/ICSI) (Daraï *et al.* 2017, Ballester *et al.* 2017, Iversen *et al.*

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2017, Bendifallah *et al.* 2017). However, clear data on the value of surgery as a fertility-enhancing procedure is lacking as is reflected by the wide range of spontaneous pregnancies after colorectal endometriosis surgery (ranging from 8% to 69%) demonstrated in the review of Iversen *et al.* (2017). Moreover, colorectal endometriosis surgery, particularly rectal surgery, is associated with a potential risk for severe morbidities (4.6–5.1%) such as lower anterior resection syndrome (LARS), infection, post-operative adhesion formation and re-operation (including temporary stoma in case of anastomotic leak or rectovaginal fistula) (Becker *et al.* 2022, Hudelist *et al.* 2022). Also, there is a risk of disease recurrence (Meuleman *et al.* 2011). The other treatment option for colorectal endometriosis-related subfertility, IVF/ICSI, is often initiated when pain symptoms are tolerable, and the patient's primary goal is to conceive. In the few studies that have been published on IVF/ICSI treatment in subfertile patients with colorectal endometriosis, live birth rate (LBR) rates ranged from 32.0% to 64.4% (Ballester *et al.* 2012, Bendifallah *et al.* 2017, Maignien *et al.* 2021). However, it is unclear whether a combined strategy could have resulted in higher LBRs, as well as evidence on the optimal timing for surgery in the treatment trajectory. Consequently, gynaecologists face difficulties in counselling to start/proceed with either IVF/ICSI or surgery, especially in patients with less prominent pain symptoms, as it is challenging to weigh the potential benefits of surgery as a fertility-enhancing procedure against to potential risks for severe morbidity (Daniilidis *et al.* 2022). Surgery may remove the source of subfertility and pain, but it can delay the start of pregnancy, resulting in a decreased ovarian reserve over time. On the other hand, IVF/ICSI seems a viable option, but prior surgery may increase the chance of conception (naturally and/or after IVF/ICSI).

At the moment, the optimal treatment to increase the chance of pregnancy and live birth in patients with colorectal endometriosis and subfertility is unknown, and this topic has been prioritized as a knowledge gap by the ESHRE Guideline Development Group and the Dutch Society of Obstetrics and Gynaecology (NVOG 2017-2020, 2023-2026, Becker *et al.* 2022). Therefore, the primary aim of this study is to determine whether surgical excision of colorectal endometriosis results in an increased live birth rate, both spontaneous and combined with IVF/ICSI, compared to an IVF/ICSI-only treatment trajectory. Secondary aims include the evaluation of patient-reported outcome measures (PROMs) and cost-effectiveness between the surgery group versus the IVF/ICSI group.

Outcomes

Primary outcome

The primary outcome is the cumulative ongoing pregnancy rate resulting in a live birth. In line with the COMMIT initiative, live birth is defined as the complete expulsion or extraction from a woman of a product of fertilisation after 20 weeks of gestational age; which, after such separation, breathes or shows any other evidence of life, such as heartbeat, umbilical cord pulsation or definite movement of voluntary muscles, irrespective of whether the umbilical cord has been cut or the placenta is attached. A birth weight of 350 g or more can be used if gestational age is unknown (Duffy *et al.* 2020).

Secondary outcomes

The secondary outcomes are listed in Table 1. A clinical pregnancy is defined as a viable intrauterine pregnancy confirmed by ultrasound with at least one fetus with a discernible heartbeat during ultrasonographic examination (Duffy *et al.* 2020). For the numeric rating scale (NRS) scores, the patient is asked to rate their pain on a scale from 0 (no pain) to 10 (worst pain imaginable). PROMs that will be administered include the EHP-30, EQ-5D-5L, LARS and the iPCQ questionnaire. The NRS scores, EHP-30 and the LARS questionnaire will be administered at baseline and 12, 24 and 36 months after inclusion. The EQ-5D-5L and the iPCQ questionnaires will be more frequently administered (EQ-5D-5L: at baseline and EQ-5D-5L and iPCQ at 6, 12, 18, 24, 30, 36 and 40 months after inclusion on $T=0$). If a patient undergoes surgery and the NRS scores, EHP-30 and LARS questionnaire were completed more than 3 months prior to the planned surgery, these questionnaires will be re-administered 1–3 weeks before surgery.

Baseline characteristics

The baseline characteristics that will be collected during the study will include demographic data and medical and obstetric history, including the following variables: age, BMI, smoking, alcohol use, comorbidities affecting fertility (e.g. PCOS), hormonal usage, prior abdominal surgery (laparoscopic or laparotomy), prior endometriosis surgery (laparoscopic vs laparotomy and diagnostic vs therapeutic), prior ovarian surgery, duration active wish to conceive (coitus without protection, no birth control) at $T=0$, primary or secondary subfertility, fallopian tube status (if available), prior fertility treatments (e.g. intrauterine insemination (IUI)), male factor subfertility, anti-Müllerian hormone (AMH) and antral follicle count (AFC) (if available and regarded representative: within prior 2 years not followed by ovarian surgery). Pre-treatment characteristics will include pain scores (chronic pelvic pain, dyschezia, dysmenorrhoea, dysuria and dyspareunia) and endometriosis classification (MRI and/or ultrasound) according to the #Enzian classification, including the presence of adenomyosis according to the MUSA criteria. The pre-surgical #Enzian classification according to MRI (or ultrasound if MRI not available) will be used to compare endometriosis classification at baseline between the surgery and IVF/ICSI-only group (Keckstein *et al.* 2021). Previous literature has shown that MRI-based #Enzian scores correlate well with

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https://doi.org/10.1530/RAF-23-0048

Table 1 Secondary outcomes.

Clinical pregnancy rate	Patients' medical file
Time to pregnancy (months)	Patients' medical file
Pain scores	NRS scores for chronic pelvic pain, dyschezia, dysmenorrhea, dysuria and dyspareunia
Endometriosis-specific symptoms	EHP-30 questionnaire
Quality of life in general	EQ-5D-5L questionnaire
Bowel-specific symptoms	LARS-score questionnaire
Surgical complications according to the CLAVIEN-DINDO grading system	Patients' medical file
IVF/ICSI treatment	Patients' medical file
Downregulation and ovarian stimulation protocol	
Number of oocytes and embryos	
Number of (cryopreserved) embryo transfers	
Fertilization rate (number of fertilised oocytes per number of retrieved oocytes)	
Implantation rate (number of embryonic sacs observed by TVS per number of transferred embryos)	
Adverse events, complications (bowel occlusion, infection, ovarian hyperstimulation syndrome and bleeding)	
Cancellation rate	
Adverse pregnancy outcomes	Patients' medical file
Miscarriage	
Ectopic pregnancy	
Still birth	
Termination of pregnancy	
Pregnancy complications	Patients' medical file
Gestational hypertension	
Pre-eclampsia	
Preterm birth	
Placenta previa	
Placental abruption	
SHiP	
Societal costs	iPCQ, medical costs (patients' medical file)
Budget impact	Total costs per treatment group adjusted for the number of IVF/ICSI cycles
Factors to be taken into account	- Patient characteristics (age, BMI, smoking, alcohol use, prior (endometriosis) surgical procedures, prior ovarian surgery, AMH (if available) - Treatment characteristics (shave/discoid excision/resection, (in)complete removal of (colorectal) endometriosis lesions, ovarian surgery, first/second/third IVF/ICSI attempt)

AMH, anti-Müllerian hormone; BMI, body mass index; EHP-30, Endometriosis Health Profile 30; EQ-5D-5L, European quality of life—five dimensions and five levels; iPCQ, Productivity Cost Questionnaire; ICSI, intracytoplasmic sperm injection; IVF, *in vitro* fertilisation; LARS, lower anterior resection syndrome; NRS, numerical rating scale; SHiP, spontaneous hemoperitoneum in pregnancy.

intraoperative findings (Burla *et al.* 2019). Expert MRI/ultrasound is available in each participating centre.

Material and methods

This protocol outlines a multicentre prospective observational cohort study. All participating centres are university and teaching hospitals in the Netherlands, all acknowledged as (candidate) level-2 centres according to the Dutch quality standard for endometriosis expertise centres (NVOG 2020). This means that a centre must adhere to various quality standards. Key criteria to become a level-2 endometriosis expertise centre in the Netherlands include: (1) maintaining a multidisciplinary team including a gynaecologist, gastrointestinal surgeon, radiologist, pain specialist, gastroenterologist, pelvic physiotherapist, psychologist and specialised nurses; (2) conducting laparoscopic resection surgeries for peritoneal, ovarian and deep endometriosis; (3) the ability to offer fertility treatments; (4) seeing a minimum of 50 new patients annually; (5) performing at least 50 endometriosis surgeries per year, with at least 20 deep endometriosis patients. In addition, centres must be actively engaged in scientific research. The level-2

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endometriosis expertise centre may function as a satellite centre for IVF or as a transport clinic (meaning that the entire IVF treatment is conducted in the respective centre, except for fertilisation and embryo transfer). This means that there is a close collaboration between endometriosis specialists and fertility doctors. Consequently, we anticipate that all endometriosis patients undergoing intake with the fertility doctor will also be evaluated by the endometriosis experts of the level-2 endometriosis expertise centre in order to provide the best counselling to optimise the chances of pregnancy.

Study population

Inclusion criteria

- Women aged between ≥21 years and ≤40 years at $T = 0$.
- Women in a heterosexual relationship or in a same-sex relationship.
- Patients with colorectal endometriosis defined as endometriosis involving the (colo)rectum (#Enzian classification score C1, C2, C3, FI (sigmoid)) diagnosed with ultrasound or MRI (Keckstein *et al.* 2021).
- Patients who have an active wish to conceive and fall under one of the following criteria:
  - at least 1 year of non-conception (either spontaneous or after intrauterine (IUI));
  - inability to have timed intercourse or to perform IUI because of pain (dyspareunia, dysuria, dyschezia, dyspareunia and/or chronic pelvic pain);
  - severe complaints (expectant management is not acceptable (anymore)).
- The patient has an indication for IVF/ICSI according to Dutch guidelines (Werkgroep netwerkrichtlijn, December 2010):
  - failed IUI;
  - male factor subfertility (oligoasthenoteratozoospermia defined as VCM (volume of ejaculate × concentration of spermatozoa × motility of spermatozoa in percentage) <1 million);
  - bilateral tubal pathology (e.g. bilateral hydrosalpinx, bilateral tubal occlusion);
  - age >38 years and (unexplained) subfertility; and
  - severe endometriosis in case of subfertility.
- Patients who are informed by their endometriosis specialist on the choice between IVF/ICSI vs laparoscopic colorectal endometriosis excision surgery at $T = 0$, $T = 1$ or $T = 2$ (Fig. 1) in their treatment trajectory (indicated by blue boxes).

Exclusion criteria

- Patients with deep endometriosis without colorectal involvement.
- Patients who conceive spontaneously prior to intervention.
- Patients requiring surgery on short notice and therefore unable to opt for IVF/ICSI (e.g. in case of unilateral or bilateral hydronephrosis, severe bowel stenosis and suspicion of an impending ileus).
- Patients with a contraindication for IVF/ICSI (e.g. diminished ovarian reserve (premature ovarian failure) (AMH (when available) <p10 adjusted for age), untreated congenital uterine abnormalities, maltreated/untreated systemic or malignant disease or severe risk factors for oocyte aspiration).
- Patients diagnosed with other diseases causing infertility (e.g. recurrent miscarriages, antiphospholipid syndrome).
- Not able to read and understand Dutch or English.

Patients experiencing severe pain symptoms, which may impair intercourse, will be included as this is a common encountered presentation in clinical practice. While these patients may not meet the official criteria of subfertility (defined as 12 months of timed intercourse without conception), the decision to lower pain symptoms either by surgery or with downregulation, in order to make it possible to pursue spontaneous conception or IVF/ICSI, is also of interest in this cohort. Patients aged over 40 will be excluded to ensure that women still have a reasonable chance to conceive spontaneously after surgery. Additionally, study participants must be able to undergo all three IVF/

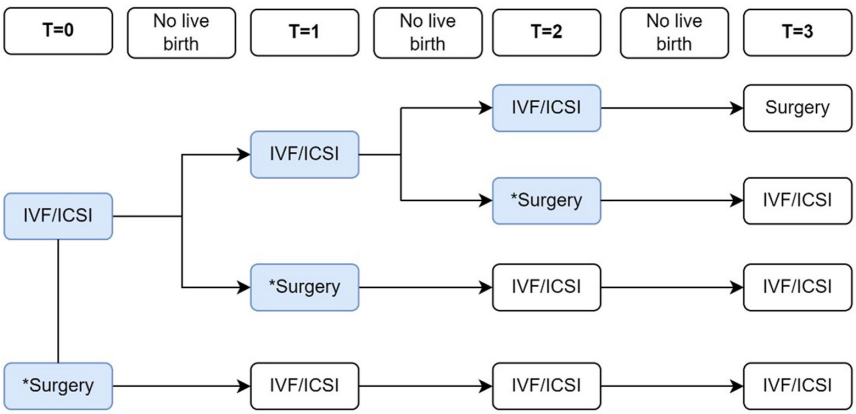

Figure 1

Treatment flow for patients with colorectal endometriosis and an unfulfilled wish to conceive. *The duration of the time to allow natural conception is determined based on the Endometriosis Fertility Index (EFI) (maximum 12 months). The EFI score will be determined based on surgical and historical factors.
ICSI = intracytoplasmic sperm injection; IVF = *in vitro* fertilization.

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ICSI procedures (if necessary), and in the Netherlands, reimbursement of IVF/ICSI treatments is granted till the age of 43 (start of hormonal stimulation). Patients aged under 21 years will also be excluded because we believe that performing IVF/ICSI and/or surgery to enhance fertility is not common practice in younger women.

Figure 2 provides a global overview of the study timeline from a patient's perspective. Patients who meet the inclusion and exclusion criteria will be verbally informed about the TOSCA study by their physician. All patients will receive an information leaflet about the potential treatment options for subfertility related to (colorectal) endometriosis and written information about the TOSCA study. The patient information and questionnaires will be available in Dutch or English. Recruitment will be on a voluntary basis, and withdrawal of consent is possible at any time without consequences for the patient's treatment. If the patient is willing to participate after a consideration period of 1 week, informed consent will be digitally obtained after which the patients receive the baseline questionnaires. The total follow-up time per patient will include 40 months unless the study endpoint (live birth) is achieved earlier. The endpoint criteria of the study are: (1) live birth or (2) no live birth after 40 months of follow-up despite IVF/ICSI (maximum three cycles), colorectal resection surgery or a combination of both treatments. The choice between surgery or IVF/ICSI treatment will be determined through shared decision-making while taking the patient's current quality of life into consideration.

IVF/ICSI will be performed according to the local protocol of each participating centre to enable implementation of the study in daily practice. The IVF/ICSI downregulation treatments and stimulation protocols will be documented. We do not expect the choice of ovarian stimulation protocol to significantly influence reproductive outcomes as studies did not show a significant difference in pregnancy or live birth rates between GnRH antagonist and agonist protocols (Becker *et al.* 2022). Patients may undergo a maximum of three IVF/ICSI cycles during the study period. An IVF/ICSI cycle is defined as the transfer of all embryos created after an ovum pickup.

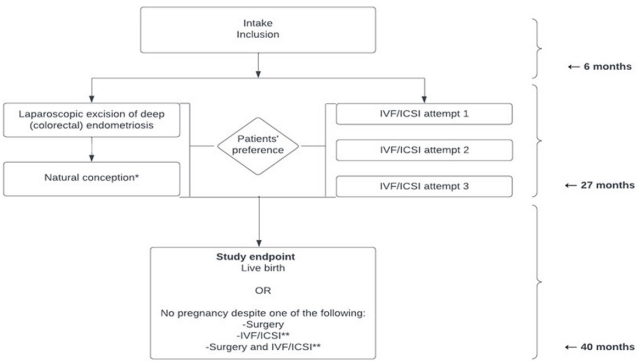

Figure 2

Flowchart of TOSCA study. *The duration of the time to allow natural conception is determined by the Endometriosis Fertility Index (EFI) (maximal 12 months). The EFI score will be determined based on surgical and historical factors; **Maximal three attempts.

Laparoscopic (colorectal) endometriosis resection and resection of other lesions (e.g. ovarian cystectomy, uterosacral ligament resection and ureterolysis) will be performed during the same procedure when indicated, as described by the working group of the European Society for Gynaecological Endoscopy, ESHRE and the World Endometriosis Society (Working group of ESGE *et al.* 2020). The objective of the surgery will be to excise all endometriosis lesions in the pelvic area, including colorectal lesion(s). If, for any reason, this is not deemed feasible (e.g. as determined by the surgeon or if the patient objects), this will be documented in the CRF. Colorectal surgery will be performed together with a specialised and experienced abdominal surgeon. Serosal shaving or superficial resection of endometriosis lesions from the bowel is performed when the endometriosis is only present within or on the serosa, without infiltrating the muscularis layer (Working group of ESGE *et al.* 2020). If the endometriosis has infiltrated the muscularis, a more radical approach such as full-thickness resection (discoid resection) or segmental bowel resection is necessary, depending on lesion(s) size, multifocality, and the degree of infiltration (Working group of ESGE *et al.* 2020). Colorectal surgery will not be subjected to further standardisation but will be conducted according to the judgment of the colorectal surgeon, enabling the study's implementation in daily practice. During the analysis phase, sub-analysis will be performed to assess whether the surgical techniques (shave, discoid resection and segmental resection) varied across treatment centres based on the severity of colorectal endometriosis (#Enzian C1, C2, C3). The 'Endometriosis Fertility Index' (EFI) will be used to predict the spontaneous pregnancy chance following surgery based on patient characteristics and surgical findings (Adamson & Pasta 2010). Women with an EFI score of 6–10 will be given the opportunity to conceive naturally for a maximum of 12 months (Vesali *et al.* 2020). Both natural conception and ART are discussed with women having an EFI score of 4–5, and the treatment choice will be based on shared decision-making and the patients' preferences (Vesali *et al.* 2020). In women with an EFI score of 0–3, IVF/ICSI will be strongly advised (Vesali *et al.* 2020). Castor EDC® will be used to collect questionnaires prospectively. Missing values are minimised through active monitoring. No additional study visits for the participants are necessary. Patients with colorectal endometriosis *in situ* during fertilisation (resulting in live birth) will be enrolled in the IVF/ICSI-only group. Those without colorectal endometriosis *in situ* during this period (who have undergone resection surgery) will be assigned to the surgery group. This means that patients in whom oocytes were retrieved prior to colorectal surgery and who underwent embryo transfer after surgery (resulting in live birth) will be categorised in the surgery group.

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Study withdrawal criteria are: (1) patient-initiated withdrawal from the study, (2) if, during surgery, it becomes evident that the endometriosis lesion is not located in the colorectal area (but in the rectovaginal area), and (3) discontinuation of the patient's intent to conceive.

Sample size

The sample size calculation is based on the expected live birth rate for IVF/ICSI-only treatment, estimated at 51.2% (after three cycles). This rate was calculated using a combination of previous published data on live births following IVF/ICSI-only treatment in 231 subfertile women, resulting in a total of 118 live births (Bendifallah 2017, Ballester 2012, Maignien 2021). The benefit of surgical treatment would have to be substantial to outweigh the risks of the procedure and was set at a 20% point increase. In the analysis phase, a minimum absolute difference of 10% in LBR in favour of the surgery group vs the IVF/ICSI-only group will be required to conclude that adding surgery to the treatment trajectory is superior to the IVF/ICSI-only treatment. Equal group sizes of 152 in both groups would be sufficient to achieve 90% power for the detection of a difference of 20% in live births with an α of 0.05. The proportion in group one (the surgery group) is assumed to be 0.51 under the null hypothesis and 0.71 under the alternative hypothesis. The proportion in group two (the IVF/ICSI group) is 0.51. With unequal group sizes and a group size ratio of 3, the sample size for the surgery group is 76, and the IVF/ICSI-only group is 228. We expect the ratio to be within these limits. In the event that the distribution of participants among the groups is more evenly balanced than initially expected, it may result in a reduced need to include a larger number of patients. Therefore, an interim analysis will be performed after the inclusion of 150 patients. Taking into account a 10% dropout during follow-up, we will include 339 patients (85 in the surgery group, 254 in the IVF/ICSI-only group) at either $T=0$, $T=1$ or $T=2$ (Fig. 1), provided that a treatment decision between ART and surgery is possible (indicated by blue boxes). We do not anticipate a high dropout rate since the study does not affect treatment decisions.

Statistical analysis

Statistical analysis will be performed using SPSS. A Shapiro–Wilk test will evaluate the distribution of the data. Dichotomous or categorical data will be presented in percentages, and continuous data as means and standard deviations (normally distributed) or medians and interquartile ranges (non-parametric). The primary outcome (cumulative LBR in the surgery vs IVF/ICSI-only group) will be assessed using a two-sided Z-test with unpooled variance. Surgical treatment (potentially combined with IVF/ICSI) will be considered superior to the IVF/ICSI-only treatment in case the cumulative LBR in the surgical group vs the ART-only group exceeds with more than an absolute difference of 10%. In addition, a survival analysis will be performed (Kaplan–Meier curves) in both groups, with live birth considered as an 'event'. Subgroup analysis will be performed in the group of patients who combined surgery and IVF/ICSI to assess the effect of the timing of surgery on the LBR. The difference in secondary outcomes between both groups will be analysed using the Student's t-test for continuous variables, the Mann–Whitney U test for non-parametric variables, and Fisher's exact or chi-square tests for categorical data. Simple and multiple regression analysis will be used to assess the correlations between live birth and patient as well as treatment characteristics (as outlined in Table 1). This approach will also allow for correction of potential confounding factors. A two-tailed P-value of <0.05 will be considered statistically significant.

Cost-effectiveness

The economic evaluation will be performed as a trial-based cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) from a societal perspective, according to the Dutch guidelines (Nederland 2016). For the CEA, the primary outcome parameter will be the cost per live birth rate. With this outcome parameter, the incremental cost-effectiveness ratio will provide data to guide the preference. For the CUA, the primary outcome will be the cost per quality-adjusted life-years based on the EQ-5D-5L scores, to provide data on the cost per QALY gained. The time horizon of the evaluation will be the period between inclusion and study endpoint (i.e. live birth or 40 months after inclusion). Discounting will be applied according to the Dutch guideline (4% for costs and 1.5% for benefits) in order to weigh future gains and losses less heavily than those that occur in the present. Multiple imputations will be used to deal with missing data. Differences in mean costs and effects (QALYs) between strategies will be compared with bootstrapping using 1000 replications. In a net-benefit analysis, costs will be related to QALYs and presented in a cost-effectiveness acceptability curve. In a cost-effectiveness acceptability curve, the probability of cost-effectiveness for surgical treatment compared to IVF will be shown for different values of the willingness to pay, including the Dutch threshold values ranging between 20,000 and 80,000 Euro per QALY (Zwaap *et al.* 2015). Sensitivity analyses will be performed to evaluate the robustness of our results. These will include analyses from a healthcare sector perspective and using EQ-VAS utilities instead of EQ-5D-5L utilities. Analyses will be performed using Stata and Excel. Both healthcare costs (secondary and tertiary care) and the cost of loss of productivity for paid and unpaid work will be included. Healthcare resource use (i.e. gynaecology visits, fertility specialist visits, visits an emergency room, hospitalisation, ambulance care, medication use) will be obtained from patients' medical files. Healthcare utilisation will be evaluated using Dutch costing manual (Hakkaart-Van Roijen *et al.* 2016).

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Medication use will be valued with prices derived from www.medicijnkosten.nl. The iPCQ questionnaire will be used to monitor absenteeism and presenteeism from paid and unpaid work.

Budget impact analysis

A budget impact analysis (BIA) to estimate the financial impact of adoption and diffusion of surgical excision at the national level will be performed. The BIA will be conducted from the perspective of the different healthcare professionals (health insurers and healthcare providers) and from the societal perspective (i.e. by including productivity costs). Costs will be estimated per budget period (1 year) for a time horizon of 40 months.

Data management

All data will be collected in Castor EDC®, a web-based clinical data management system. Data processing will be done according to the EU General Data Protection Regulation and the Dutch Act on the implementation of the General Data Protection Regulation (in Dutch: Uitvoeringswet AVG). Analysis of the data will be performed with the coded data. The key that links the code to personal patient information will only be available to the local study team in each centre. Data will be stored for 15 years.

Focus group

An online focus group was conducted to assess the feasibility of patient participation and comprehensibility of patient information among six women diagnosed with colorectal endometriosis, who underwent IVF and/or laparoscopic colorectal endometriosis resection in the past 5 years due to endometriosis-related subfertility. Participants were recruited by their gynaecologists at participating centres ($n = 2$) and through advertisements on the social media account of the Dutch Endometriosis Patient Federation ($n = 4$). Prior to the focus group, participants received all patient information and an overview of the PROMs that will periodically be sent to patients participating in the TOSCA study. The focus group was directed by a moderator (RdK) and an observer (MB) monitoring the process, while the chair of the Dutch Patient Federation (BdB) was present to provide support. A semi-structured interview was carried out to allow participants to freely share their experiences. Participants provided informed consent prior to the session, and anonymity and confidentiality were ensured. The session was audio-ecorded and fully transcribed for analysis. RdK and MB analysed the transcript of the focus group individually to identify the most important themes. The results of the focus group can be found in the Supplementary Data section.

Ethical approval

This study is registered as the TOSCA study on clinicaltrials.gov (NCT05677269). The LDD Medical Research Ethics Committee has approved this study (Ref. No. N22.085).

Discussion

The most effective treatment approach to improve the LBR in women with colorectal endometriosis and subfertility is unknown. This knowledge gap has been prioritised by the ESHRE Guideline Development Group and the Dutch Society of Obstetrics and Gynaecology (Becker *et al.* 2022, NVOG 2017–2020, NVOG 2023–2026). The current lack of evidence impairs gynaecologists from providing adequate counselling and shared decision-making, as women may only be informed about potential surgical complications, rather than the potential benefits of surgery with regard to fertility.

The TOSCA study will compare surgery (potentially combined with IVF/ICSI) vs IVF/ICSI-only treatment in women with colorectal endometriosis and subfertility, in order to provide evidence on the value of surgery as a fertility-enhancing procedure.

Previous literature demonstrates a negative effect of the presence of colorectal lesions on reproductive outcomes (Stepniewska *et al.* 2009). However, the value of laparoscopic removal of these lesions to improve the chance to conceive (naturally) is unclear due to heterogeneous results from low-quality studies (Iversen *et al.* 2017). This review reported a spontaneous pregnancy rate (SPR) after surgery of 49% (ranging from 21% to 69%, $n = 136$ patients) in four retrospective studies and 21% (ranging from 8% to 50%, $n = 184$ patients) in three prospective studies (Iversen *et al.* 2017). However, these studies did not include LBR as an outcome. Other studies examining the effect of IVF/ICSI-only treatment in women with colorectal endometriosis-related subfertility did include LBR as an outcome and reported an LBR ranging between 32% ($n = 75$), 54.9% ($n = 55$) and 64.4% ($n = 101$) (Maignien *et al.* 2021, Bendifallah *et al.* 2017, Ballester *et al.* 2012). The question remains whether a combined strategy (surgery and IVF/ICSI) results in even higher LBR compared to IVF/ICSI-only treatment. In addition, the optimal timing of surgery in the treatment trajectory is not clear. One retrospective matched cohort study ($n = 110$ patients), comparing the LBR between surgery followed by ART vs ART-only in colorectal endometriosis patients, showed a higher LBR when ART was preceded by surgery compared to ART-only treatment (70.6% vs 54.9% at the third cycle) (Bendifallah *et al.* 2017). This is supported by a review and meta-analysis which demonstrated better reproductive outcomes in patients with colorectal involvement who underwent surgery before IVF compared to women who did not undergo surgery (OR 2.43) (Casals *et al.* 2021). However, the data used in this review were retrieved

from the same single publication of Bendifallah *et al.*, highlighting the limited availability of data on this topic. In addition, the majority of studies lack information regarding colorectal endometriosis disease severity (e.g. classification and performed surgical procedure) or an IVF/ICSI-only (control) group, and therefore the conclusions that can be drawn are hard to adopt into the counselling of the patient. It is evident that a well-designed study is necessary to provide evidence-based data that are directly transferable to clinical practice. The TOSCA study will provide a unique cohort for long-term follow-up to gain prospective knowledge about reproductive outcomes and about the cost-effectiveness of surgery (potentially combined with IVF/ICSI) vs IVF/ICSI-only treatment.

The TOSCA study compares two treatments that are part of the standard care to treat subfertile patients with colorectal endometriosis. Therefore, study participants will not be subjected to additional risks. The only potential obstacle for patients to participate in the TOSCA study is the requirement to complete questionnaires every 6 months. However, the feasibility of patient participation in the TOSCA study was assessed in a focus group, which revealed that participants did not identify any impediments for women to participate in the study (Supplementary data, see section on supplementary materials given at the end of this article).

The TOSCA study has notable strengths. To the best of our knowledge, it is the first adequately powered prospective trial that directly compares surgery (potentially combined with IVF/ICSI) to IVF/ICSI-only treatment in order to provide a definite answer to the question of whether surgical excision of colorectal endometriosis is of additional value, not only in terms of enhancing quality of life but also in relation to reproductive outcomes. In addition, the TOSCA study will be conducted in multiple specialised endometriosis centres across the Netherlands, ensuring results that are representative of daily practice while maintaining a high standard of endometriosis care.

Limitations of the study include that AMH is not a standardised variable that will be collected at baseline. This is not possible due to lack of funding for this study. However, we anticipate that AMH values will be available from the majority of included women (depending on the standard of care per endometriosis/fertility centre). In addition, the study is susceptible to potential confounders (as outlined in Table 1) since patients will not be randomised between treatment groups. Nevertheless, we will correct for these potential confounding factors using multiple regression analysis. Randomised controlled trials (RCTs) have long been presumed as gold standard for studying causal interference (Deaton & Cartwright 2018). However, one in five surgical RCTs are discontinued early, with poor recruitment being the most common reason (44%) (Chapman *et al.* 2014). Particularly challenging are trials comparing surgical and non-surgical interventions. The idea that such different interventions may result in similar long-term outcomes when the short-term side effects are very different may hamper patients from participating in a clinical trial as patients often desire to exert their own preferences when making treatment decisions (Paramasivan *et al.* 2011). This could explain why the ENDOFERT study (clinical trials.gov ref. nr. NCT02948972), which has been recruiting patients with colorectal endometriosis-related subfertility since 2016 to randomise between surgical removal of colorectal endometriosis and subsequent IVF and IVF-only treatment, is still recruiting. For this reason, it is also questionable whether the EFFORT study, an RCT initiated by the same research group (clinical trials.gov ref. nr. NCT04610710), will meet its recruitment target. Also, we are still awaiting the publication of the definitive results from the FERTILITY-RECTOSIGMOID study, which was presented at a congress in 2022 (Barra *et al.* 2022). It is time for the scientific community to acknowledge that other methodologies may be more feasible and equally sufficient in addressing research questions. In addition, one could also question whether trial participants in an RCT are representative for the population as a whole. We believe that the current patient preference design matches the target patient population and the Dutch healthcare system and justifies our study objective.

The TOSCA study will provide evidence-based data on the value of colorectal endometriosis surgery as a fertility-enhancing procedure. In addition, the study will establish a unique cohort for long-term follow-up, providing valuable prospective knowledge on the cost-effectiveness of surgery vs IVF/ICSI-only treatment and the respective effects of these treatments on patients' quality of life.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/RAF-23-0048.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the protocol presented here.

Funding

No grants were received to conduct the TOSCA study. All hospitals participated due to the relevance of this study. They did not receive any financial compensation for their involvement.

Author contribution statement

MB and AC designed the study in collaboration with all authors. RdK set up the study together with all local investigators under supervision of MB. RdK, MB and BdB conducted the focus group. RdK drafted the manuscript with MB. HG performed the sample size calculation. All authors contributed to revising the manuscript and provided approval for the final version for publication.

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