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EFFORT study: Comparing impact of operation and assisted reproductive technologies on fertility for women with deep infiltrating endometriosis – study protocol for a multicentre randomised trial

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ABSTRACT

Introduction Deep infiltrating endometriosis (DIE) affecting the rectum or sigmoid colon is associated with infertility, severe pain and decreased quality of life. As most women with DIE are young, many have a pregnancy intention. Treatment possibilities of endometriosis-associated infertility are surgery or assisted reproductive technologies (ART). However, no studies have compared the two interventions directly. Therefore, this study aims to determine the cumulative pregnancy rate (CPR) and the live birth rate (LBR) after first-line surgery compared with first-line ART for women with rectosigmoid DIE and a pregnancy intention.

Methods and analysis Multicentre, parallel-group, randomised trial of women with rectosigmoid DIE and a pregnancy intention for at least 6 months in Aarhus, Denmark and Bordeaux, France. 352 women aged 18–38 years are randomised 1:1 to either surgical management (shaving, disc excision or segmental resection) or ART management (at least two in vitro fertilisation or intracytoplasmic sperm injection procedures if not pregnant after the first cycle). Women in the surgical intervention group will attempt to get pregnant by either spontaneous conception or ART, depending on the endometriosis fertility index score. Primary outcome measures are CPR and LBR at 18 months' follow-up. Secondary outcomes are: Non-viable pregnancies, time to pregnancy, pain score, quality of life, complication rate, bowel and bladder function, endocrine and inflammatory profile, number of oocytes, blastocysts, frozen embryos and blastocyst morphology score within 18 months after either intervention.

Ethics and dissemination Conduct of this study is approved by the Danish National Committee on Health Research Ethics and Comité de Protection des Personnes Ile de France VIII. Study participants must sign an informed consent form. The results will be presented at national and international conferences and published in international peer-reviewed journals.

Trial registration number This trial is registered at ClinicalTrials.gov (no. NCT04610710).

Protocol version The Danish National Committee on Health Research Ethics: Fifth protocol version approved 7 September 2020 (no. 1-10-72-96-20). Comité de Protection des Personnes Ile de France VIII: Version 1.1 22JAN2021 the 9 March 2021.

Strengths and limitations of this study

- This study is conducted as a multicentre, randomised controlled trial comparing surgery to assisted reproductive technologies for women with deep infiltrating endometriosis and an intention to become pregnant.
- Broad inclusion criteria ensure great generalisability of the study results.
- Outcomes will offer clinically relevant insight regarding ongoing treatment of endometriosis-associated infertility.
- Blinding has not been possible due to the nature of both interventions.
- Because a large sample size is required, participant recruitment within our time frame could become challenging.

INTRODUCTION

Deep infiltrating endometriosis (DIE) is a benign gynaecological condition characterised by the presence of ectopic endometrium-like tissue that grows >5 mm into the peritoneum and can affect the sigmoid or rectum.[1] DIE is associated with infertility, decreased quality of life and chronic pelvic pain including dysmenorrhea, dyschezia and dyspareunia.[2–4] Women with DIE often have a pregnancy intention. Therefore, conception should not be delayed by prolonged treatment of endometriosis-associated infertility, as this may result in decreased ovarian reserve with time.[5 6] Thus, choosing the right treatment for each woman is crucial.

Up to 40% of women attending a fertility clinic have endometriosis.[7] Choice of first-line

treatment of infertility caused by endometriosis is often by assisted reproductive technologies (ART), such as in vitro fertilisation (IVF).[8 9] IVF has been shown to increase the fertility rate in these women,[10] but has no or in some cases even a detrimental effect on pain symptoms.[11 12]

Surgical treatment of rectosigmoid DIE comprise laparoscopic shaving, disc excision or colorectal resection.[13] These surgeries have been shown to increase quality of life after 12 months.[14] At the same time, there seems to be up to 57% of these women, who can obtain a spontaneous pregnancy after such surgery.[15] Laparoscopic rectosigmoid resection for a benign disease is, however, a large operation that carries a 10%–12% risk of complications including anastomotic leakage resulting in a temporary stoma, rectovaginal fistula, pelvic abscess, urinary retention and/or decreased ovarian reserve.[13 16 17]

The clinical question is how to advise women with DIE who wish to become pregnant. If spontaneous pregnancy is not achieved within a reasonable time (of 6 months), should the women go for surgery or ART? So far, no studies have addressed this question, and both endometriosis surgeons and fertility doctors seek answers to these questions.[18 19] This study, therefore, investigates the cumulative pregnancy rate (CPR) and the live birth rate (LBR) in women with DIE affecting the colorectum after either first-line surgery or first-line ART as described below in a multicentre, parallel-group, randomised setting.

Objectives

Primary objective

The primary objective is to compare CPR and LBR 18 months after first-line surgery to first-line ART for women with DIE and a pregnancy intention. Women in the surgical intervention arm will try conception either spontaneously and/or by ART after the surgery. We hypothesise an increased CPR and LBR by first-line surgical intervention compared with first-line ART intervention.

Secondary objectives

1. To compare self-reported quality of life and pain score for women with DIE and a pregnancy intention after first-line surgery to first-line ART after 9 and 18 months.
2. To determine complication rate within 18 months after complete surgery for DIE in the first-line surgical intervention arm and after ART in the first-line ART intervention arm.
3. To investigate delayed functional bladder and bowel morbidity after first-line surgery and first-line ART at 9 and 18 months after intervention.
4. To measure and compare time to pregnancy (TTP) within 18 months from intervention to first ongoing pregnancy after first-line surgery to first-line ART.
5. To compare blood inflammatory markers and hormonal profiles prior to and after first-line surgery to first-line ART management.

METHODS

Study setting

This study is conducted as a multicentre, parallel-group, randomised trial. Study participants will be recruited at the two surgical sites: The Department of Obstetrics and Gynaecology at Aarhus University Hospital (AUH) in Denmark and the Endometriosis Centre, Clinique Tivoli-Ducos in Bordeaux, France. In Denmark, ART management will primarily be carried out at the Fertility Clinic Horsens but also other fertility clinics, including both public and private clinics. Likewise, in France, ART management will be carried out at different public and private fertility clinics, however, at no particular primary fertility clinic site. Participant recruitment began October 2020 and is expected to continue until December 2024.

The EFFORT study protocol is developed following the Standard Protocol Items: Recommendations for Interventional Trials guidelines.[20]

Patient and public involvement

This study protocol was initiated and structured without patient and public involvement due to extensive experience with DIE patient perspective and the routine care interventions at both involved centres.

Study participants and eligibility criteria

The number of study participants based on power calculation is 352 women randomised 1:1 in the intervention arms. To participate in the study, the women must meet the inclusion criteria: aged 18–38 years, rectosigmoid endometriosis and candidate for colorectal DIE surgery, pregnancy intention for at least 6 months, anti-Müllerian hormone (AMH) above 5 pmol/L, male partner and a maximum of two previous IVF treatments (number of previous intrauterine inseminations is not limited). The woman will be excluded in case of unilateral or bilateral hydronephrosis due to endometriosis (randomisation is unethical), body mass index above 32 kg/m^2, contraindication for IVF (untreated uterine factor infertility, maltreated/untreated systemic or malignant disease or severe risk factors for oocyte aspiration), or if she does not intend to be randomised.

Recruitment of eligible participants will be at the first consult after referral for DIE and eligibility for surgery. Rectosigmoid DIE is confirmed by transvaginal ultrasound and/or a pelvic MRI scan. If the woman is a candidate for complete DIE surgery and has a pregnancy intention, she will be asked to participate in the study. The study will be carefully explained during the consultation, and she will receive written participant information and a consent form. Study information will be given by the gynaecologist.

Study plan and randomisation

Study participants with signed consent forms will be enrolled in the study time plan as shown in figure 1.

Study participants are randomised (1:1) to either of two intervention arms: Group A is first-line surgical

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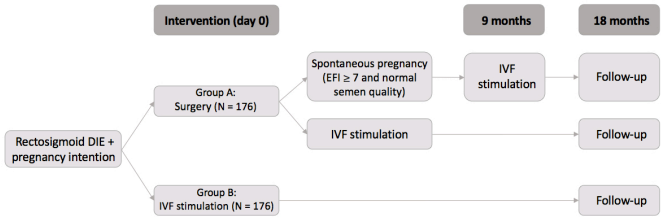

Figure 1 Study time plan and follow-up study points for primary and secondary outcomes data acquisition. DIE, deep infiltrating endometriosis; EFI, Endometriosis Fertility Index; IVF, in vitro fertilisation.

intervention with rectosigmoid DIE operation and Group B will receive first-line IVF treatment (at least two procedures if not pregnant after the first). Intervention time point is defined as the surgery date in Group A and as the first day of follicle-stimulating hormone (FSH)/human menopause gonadotropin (hMG) administration in group B. The partner must have a semen quality acceptable for spontaneous conception (≥one million total semen in the raw specimen independent of motility). Women in Group A will be divided into two categories based on mode of conception postoperatively. If the Endometriosis Fertility Index (EFI) is ≥7, the woman will attempt spontaneous conception for 9 months. If EFI<7, the woman will receive IVF directly after surgery. After 9 months of unsuccessful spontaneous conception attempt, IVF management will routinely be proposed. Referral for ART will be in a well-timed manner, so the woman can begin treatment at 9 months postoperatively. Follow-up for all study participants in both arms is 9 months (M9) and 18 months (M18) after each intervention.

Randomisation

Randomisation is stratified by centre. To ensure equal distribution of study participants in both intervention arms during the entire study time plan, block randomisation was performed. However, due to predictability of intervention allocation, information on block size will not be available during the study period. A stratified block randomised allocation table has been made in R (R Core Team) using a computer-generated random number sequence. This allocation table is uploaded to the randomisation module in Research Electronic Data Capture (REDCap). Allocation to either intervention group of each study participant is final and locked after randomisation. No blinding is possible with the interventions.

Interventions

Operative procedure

Surgical treatment for rectosigmoid DIE is by minimally invasive laparoscopic shaving, colorectal segmental resection or disc excision. The extent of resection of the bowel nodule will depend on the size of the nodule and feasibility. All other visible endometriosis will also be removed at the operation. All bowel resections will be performed by specialised gynaecologist in collaboration with specialised colorectal surgeons. Both the centres in Bordeaux and in Aarhus are tertiary referral centres for advanced endometriosis operations. Both centres have documented their expertise.[14 21 22] All operative details regarding operative time, postoperative complications and the extent of resections will be recorded. All tissue removed will be send for pathological examination.

IVF stimulation protocol

Fertility treatment is preferably with a standard gonadotropin-releasing hormone (GnRH) agonist protocol (if needed, up to 3 months of pretreatment with GnRH agonist can be used). Ovarian stimulation will be with menotropin (hMG) with a dose according to clinic standard. Induction of ovulation will be with human chorionic gonadotropin (hCG) triggering when≥3 follicles are ≥17 mm (unless fewer follicles are present). Oocyte pick-up (OPU) will be performed 34–36 hours later. According to semen quality on the day of OPU, the fertilisation will be done by IVF or intracytoplasmic sperm injection. One blastocyst will be transferred, preferably on day 5. On day 14–16 after OPU a blood sample of hCG will be taken to evaluate the result of the stimulation. Within the 18 months' follow-up, number of follicles at last scan prior to OPU, number of oocytes retrieved at OPU, number of fertilised oocytes, number of blastocysts and the morphology scores according to the Gardner scoring system will be compared.

If this fertility protocol is not possible to follow for IVF (especially for French fertility clinics), other protocols or interventions are accepted, e.g. antagonist protocols and/or transfer of cleavage stage embryos on day 2 or 3 after OPU. Also, other blastocyst scoring systems are accepted, for example, Steer and Veecks criteria, respectively.

Questionnaire

Study participants are asked to answer a questionnaire at three different study points: At baseline, at M9 and at M18. The questionnaire will contain questions on demographic information, known diseases, medication, smoking habits and alcohol consumption, previous surgery, sexual activity, previous pregnancies and previous fertility treatment. Furthermore, patient-reported outcome measures (PROMs) will be used for:

- Pain score at time of filling in the questionnaire with Numeric Rating Scale (NRS).
- Quality of life and sexual function in the last 4 weeks prior to filling in the questionnaire with Endometriosis Health Profile 30+23 (EHP-30 +23).[23]
- Bowel function in the last month prior to filling in the questionnaire with Low Anterior Resection Syndrome (LARS) score.[24]
- Bladder function in the last month prior to filling in the questionnaire with the International Consultation on Incontinence Questionnaire (ICIQ-FLUTS).[25]

Questionnaires at M9 and M18 will only contain the above-mentioned PROMs.

Blood sampling

At baseline, blood samples of hormone values are necessary to establish fertility status for each woman. These hormonal values include AMH, FSH, luteinising hormone, estradiol (E2), thyroid-stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), thyroid peroxidase antibodies and TSH receptor autoantibodies (TRAb), which are usually part of a routine check-up prior to ART. Furthermore, to determine endometriosis inflammatory status before and after either intervention, the baseline blood sample will include the inflammatory markers: tumour necrosis factor alpha, interleukin 1β (IL-1β), IL-4, IL-6, IL-8, IL-10, IL-17, transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF) and intercellular adhesion molecule 1 (ICAM-1) for the Danish study population.[26]

The other blood sample at M18 after either intervention will be measuring AMH as a variable for ovarian reserve. The M18 blood sample will also include other hormones and inflammatory status in the Danish study population.

Each study participant will have two blood samples drawn in relation to the study. The first blood sample is taken at baseline at day 2–day 5 in the beginning of the menstrual cycle, as the hormone values are cycle dependent. The second blood sample is taken 9–18 months after either intervention depending on whether the woman has become pregnant or not, as especially AMH values are influenced by pregnancy. Blood sample overview is illustrated in table 1.

Blood samples for hormonal status will be analysed immediately. Biological material (10 mL serum) for inflammatory status will be processed and stored in a freezer as a research biobank at the Department of Clinical Biochemistry at AUH, Denmark. In case of excess blood sample material after analysis, the frozen samples with only participant-specific project ID will be kept in a research biobank as backup for analysis. The stored biological material will be destroyed at the end of the study or no later than within ten years from study initiation.

Outcome measures

Primary outcome measure is CPR and LBR at 18 months after intervention. Pregnancy is defined as a fetal heartbeat by ultrasound at gestational week 6–8. Secondary pregnancy outcomes including number of biochemical pregnancies, miscarriages, missed abortions, extrauterine pregnancies and pregnancies of unknown location will be investigated and compared in the first-line surgical to first-line ART intervention group within 18 months. TTP is recorded within 18 months and defined as the time from intervention date to date of visualisation of the first ongoing pregnancy. Changes in self-reported outcome measures including pain score (NRS), quality of life (EHP-30), fertility quality of life (Section F in EHP-23), sexual function (Section C in EHP-23), delayed bowel function (LARS) and delayed bladder function (ICIQ-FLUTS) will be determined and compared at baseline, at M9 and at M18. Ovarian reserve status defined by AMH levels are compared at baseline and at M9-18 in both intervention arms. Complication rate in both intervention arms will be determined within 9 and 18 months after intervention. Complication rate in the surgical intervention arm is based on the Clavien-Dindo Classification categorising postoperative events in regard to necessity and level of therapy.[27] Postoperative complications include anastomotic leakage or stenosis, ureteral lesion or obstruction, pelvic abscess, fistula, bladder or bowel perforation and urinary retention. ART complications are defined as ovarian hyperstimulation syndrome, infection, bleeding and hospitalisation caused by an IVF procedure and worsening of pain. Within 18 months after each intervention, number of follicles as measured at last scan prior to OPU, number of oocytes at OPU, fertilised oocytes, blastocysts and frozen embryos will be recorded. In addition, blastocyst morphology score will be compared.

Finally, in the Danish study population changes in hormonal and inflammatory status will be compared at baseline and 9–18 months after intervention.

Data management and sharing

The database is managed in the secure web-based application REDCap with study participant record IDs and an

Table 1 Blood sample overview

	Danish study population	French study population
Baseline Prior to treatment	► Hormonal status (AMH, FSH, LH, E2, TSH, T3, T4, TPO, TRAb) ► Inflammatory markers (TNF-α, IL-1β, IL-4, IL-6, IL-8, IL-10, IL-17, TGF-β, VEGF, ICAM-1 etc.) ► Excess blood sampling material for research purposes	► Hormonal status (AMH, FSH, LH, E2, TSH, T3, T4, TPO, TRAb)
M18 After treatment (9–18 months)	► Hormonal status (AMH, FSH, LH, E2, TSH, T3, T4, TPO, TRAb) ► Inflammatory markers (TNF-α, IL-1β, IL-4, IL-6, IL-8, IL-10, IL-17, TGF-β, VEGF, ICAM-1, etc.) ► Excess blood sampling material for research purposes	► AMH

AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone; LH, luteinising hormone ; TNF, tumour necrosis factor; TSH, thyroid-stimulating hormone.

integrated audit trail. Logging registry in the audit trail can be accessed and reviewed at any time. An electronic case report form will be created per patient. Data entry is maintained by MR in Aarhus and two study coordinators in Bordeaux. Survey data are directly captured in the database with no additional data entry by the research group for self-reported outcome measures. All data will be pseudomised for statistical analyses and publication of research results. Personal data are handled so it complies with the Data Protection Regulation and the Data Protection Act. Ownership of data and publication of results is based on a collaboration agreement between the participating centres in Denmark and France.

At the end of participant inclusion, pseudomised study data can be shared according to the ICJME guidelines, when relevant research objectives and hypotheses are provided. Approval by Central Region Denmark and the Danish Data Protection Agency are required prior to data sharing. Request for data sharing can be directed at ubk@dadlnet.dk. The requesting party shall cover the costs for data sharing.

Statistical methods

Sample size

The number of participants is based on a power analysis. Calculations were made with different assumptions and were based on the smallest relevant differences that we expect to observe, although actual differences may well be greater. Based on reasonable assumptions of a cumulative chance of pregnancy within 18 months between 70% in the first-line surgery group and 55% in the first-line IVF group, power (1-β)=0.80, and α=0.05, the required number of participants will be 176 in each group.

Statistical analyses

The analyses will be performed according to the intention-to-treat principle. If any statistically significant differences are found between groups at baseline, adjusted analysis will be performed.[28] Subsequently, per-protocol analyses will be performed. Normally distributed, continuous variables will be presented as mean values with SD and compared using Student's t-test. Categorical outcomes will be presented as proportions and tested with χ^2 or Fisher's exact test as appropriate. Subgroup analysis of responders and non-responders will be performed. Risk factors for CPR and LBR in the two groups will be tested with multivariate logistic regression analyses. A two-sided p value of 5% will be used as level of significance. Analyses will be performed using Stata and R.

Study participant lost to follow-up will be considered not pregnant in the main analyses. Incomplete data for the primary objective will be considered not pregnant. The study participants lost to follow-up will not be replaced, as the analyses are based on intention to treat. No interim analyses will be performed.

ETHICS AND DISSEMINATION

Both interventions are routine care in treatment of endometriosis-associated infertility. Therefore, no additional harms are present in relation to participation in the study other than minor transient discomfort by the two blood samples.

All study participants must after oral and written information on the study sign a consent form prior to participation and randomisation. The study including the research biobank has been approved by the Danish National Committee on Health Research Ethics (fifth protocol version approved 7 September 2020, no. 1-10-72-96-20). Conduct of the study has been notified and approved by Central Region Denmark (no. 1-16-02-265-20). Likewise in France, Comité de Protection des Personnes Ile de France VIII approved the protocol (V.1.1, 22 January 2021 and 9 March 2021). Any modifications to the protocol will be notified and reviewed by both research ethics committees following regulations for research in the respective country.

All results—positive, negative or inconclusive—from the study will be presented at national and international conferences and published in international high-impact peer-reviewed journals.

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Contributors UBK, USK and MS-H participated in the conception and initiation of the study. HR and MR contributed to the design, writing and editing of the study protocol. MR, MS-H, HR, UBK and USK will participate in recruitment of patients and acquisition of data. UBK and MR were responsible for the blood test arrangements. MR wrote the first draft of this manuscript with input from all authors. USK has written the statistical analyses paragraph. UBK, HR, USK and MS-H were all involved in critical revision of the manuscript. All authors approved the final version of the manuscript submitted.

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Disclaimer The funders had no influence on study design, trial conduct, results or manuscript. Positive as well as negative and inconclusive study results will be published in accordance with the protocol.

Competing interests UBK has received institutional funding targeted for this study by IBSA Nordic, and institutional funding by Ferring Pharmaceuticals and Merck A/S for departmental research activity. HR has received consultant fees for training involvement by Olympus, Karl Storz, PlasmaSurgical and Ethicon.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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