CHIEF SCIENTIST OFFICE

CODE: PCL/19/01

RESEARCH PROJECT BRIEFING

Precision treatment and drug repurposing to reduce endometriosis-associated pain in women

AIMS

Endometriosis affects one in 10 women and those assigned female at birth. It is a condition where cells similar to those lining the womb (the 'endometrium') grow elsewhere in the body, forming 'lesions'. Most commonly the lesions grow on the lining of the pelvic cavity, called the peritoneum. This type of endometriosis is called superficial peritoneal endometriosis. Endometriosis can cause debilitating pain and infertility. Current treatments for endometriosis include surgery to remove the lesions, and hormone treatments that stop the ovaries producing estrogen. There is an unmet need for effective evidence-based treatments, including non-hormonal approaches.

Diagnostic laparoscopy (keyhole surgery) is the only way to confidently diagnose superficial peritoneal endometriosis. Surgical removal of endometriosis is frequent carried out at the same time as a diagnostic laparoscopy. Lesions can either be destroyed with electricity (ablated) or cut out (excised) Surgery for endometriosis carries risks, does not always work, and sometimes needs to be repeated. We don't have reliable evidence of the effectiveness of surgery for superficial peritoneal endometriosis to improve pain, with which to help patients to make a decision about their treatment.

Only one third of women feel that hormone treatments they have used for their endometriosis pain are helpful and many experience unpleasant side effects. Previous research from our group at the University of Edinburgh have identified that superficial peritoneal endometriosis is associated with high levels of lactate in the lesions and in the fluid in the peritoneal cavity. We found that dichloroacetate (DCA), a drug which lowers lactate levels and is used to treat metabolic acidosis in children, can shrink lesions in laboratory models of endometriosis

This CSO-funded clinical lectureship aimed to deliver two pilot studies:

- A surgical trial to determine feasibility of a larger trial to determine if laparoscopic treatment of superficial peritoneal endometriosis is effective at reducing endometriosis-associated pain? (**ESPriT1**)

- A medical trial to determine feasibility of a clinical trial of DCA to treat endometriosis-associated pain (**EPiC1**)

KEY FINDINGS

ESPriT1

- ESPriT1 met its minimum target for recruitment (primary outcome).
- Progress to randomisation within the trial was hampered by the Covid-19 pandemic, but all of the randomised participants returned 12-month outcome data and remained blinded until the end of their study participation.
- The majority of participants described their trial experience favourably.

EPiC1

- EPiC1 met its minimum target for recruitment and retention (co-primary outcomes).
- 79% of participants described the trial as a positive experience.
- Whilst the study was too small to determine if DCA is truly effective, the majority of participants had improvement in pain score and quality of life, and used less pain killers.

WHAT DID THE ESPriT1 STUDY INVOLVE?

Patients with suspected superficial peritoneal endometriosis undergoing diagnostic laparoscopy were recruited over a 16-month recruitment period in three Scottish centres. If superficial endometriosis was seen they were randomised in equal numbers to either surgical removal of endometriosis at the same time, or diagnostic laparoscopy only. The way in which the endometriosis was removed (excision or ablation) was at the operating surgeon's choice. Participants were told their endometriosis diagnosis, but were not told (blinded) to which group they had been allocated to until 12 months later. Participants were followed up by online questionnaires at three, six- and 12-months following surgery, assessing pain, physical and emotional function, including the condition specific Endometriosis Health Profile-30 questionnaire (EHP-30). An acceptability questionnaire was completed at 12 months. The study design was informed by a PPI panel who also gave feedback on the patient facing materials.

We calculated the proportion of confirmed eligible patients who consented to the trial, the number of participants who underwent surgery and were randomised, and the number of randomised participants who were followed up to 12 months.

Trial registration no: NCT04081532. Funder CSO TCS/18/43

The trial protocol has been published: **Whitaker LHR**, Doust A, Stephen J, Norrie J, Cooper K, Daniels J, Hummelshoj L, Cox E, Beatty L, Chien P, Madhra M, Vincent K, Horne AWH. Laparoscopic treatment of isolated superficial peritoneal endometriosis for managing chronic pelvic pain in women: study protocol for a randomised controlled feasibility trial (ESPriT1*). Pilot Feasibility Stud.* 2021; 7(1):19.

WHAT WERE THE ESPriT1 RESULTS AND WHAT DO THEY MEAN?

Between October 2019 and February 2021, 31% of eligible patients approached consented to randomisation (55/179). The most common reason given for declining participation was a preference to have endometriosis treated at the same time as diagnostic laparoscopy. Of those who consented to study, 24 underwent surgery, 3 withdrew prior to surgery and 28 remained on the surgical waiting list at the end of study. 7/24 (29%) were randomised, and the other 17 participants were ineligible at the time of surgery (14 had no endometriosis and 3 had significant adhesions, or ovarian/deep endometriosis). There were no intraoperative complications. All of the randomised participants returned 12-month outcome data and did not discover whether their endometriosis had been removed until the end of their study participation. The majority of randomised participants (6/7) described their trial experience favourably. As the study was very small the change outcomes such as pain and other symptoms, quality of life and painkiller use is not reported yet, but will be included in an individual patient data meta-analysis in combination with the ESPriT2 results, and published then.

The COVID-19 pandemic impacted considerably on the progress of our trial because all elective gynaecological surgery was paused for six months during the recruitment phase, and following resumption of recruitment there was significant restrictions to elective gynaecological surgery for non-cancer conditions.

WHAT IMPACT COULD THE ESPriT1 FINDINGS HAVE?

- We have demonstrated feasibility of recruitment to a blinded randomised controlled trial to assess efficacy of surgery for superficial peritoneal endometriosis.
- This study has informed the design of and enabled us to secure funding for our currently recruiting definitive multicentre trial (ESPriT2).
- ESPriT2 will allow us to determine the effectiveness of laparoscopic removal of superficial peritoneal endometriosis for the management of chronic pelvic pain in women (see www.ed.ac.uk/centre-reproductive-health/esprit2). This will have implications for provision of services for superficial peritoneal endometriosis.

WHAT DID THE EPiC1 STUDY INVOLVE?

Patients with a surgical diagnosis of superficial peritoneal endometriosis in the preceding 10 years were recruited from gynaecology clinics in NHS Lothian. Participants received oral DCA for 12 weeks (6.25mg/kg twice daily, increasing to 12.5mg/kg twice daily after six weeks depending on response). Participants completed online questionnaires at baseline, six- and 12-weeks assessing pain, physical and emotional function, including the condition specific Endometriosis Health Profile-30 questionnaire (EHP-30). DCA levels were monitored at one-, 6- and 12-weeks. The study design was informed by a PPI panel who also gave feedback on the patient facing materials.

The primary outcome was recruitment and retention. Secondary outcomes included compliance, side-effects and acceptability. Trial registration No: NCT04046081. Funder MRC/CIC/58

The trial protocol has been published: Leow HW, Koscielniak M, Williams L, Saunders PTK, Daniels J, Doust AM, Jones MC, Ferguson GD, Bagger Y, Horne AW, **Whitaker LHR**. Dichloroacetate as a possible treatment for endometriosis-associated pain: a single-arm open label exploratory clinical trial (EPiC). Pilot Feasibility Stud. 2021; 7(1):67

WHAT WERE THE EPiC1 RESULTS AND WHAT DO THEY MEAN?

Between November 2019 and June 2021 93 patients were approached and 30/54 eligible patients were recruited. 29/30 commenced treatment. Retention met pre-specified criteria. Return of the EHP-30 questionnaire at final visit was 90% (27/30) and 85% (128/150) of all study visits were completed. 69% (20/29) of participants completed all 12 weeks of treatment. Of the other 9, 2 stopped treatment early due to pregnancy, 2 due to side-effects, 5 were stopped in the context of the Covid-19 pandemic (including 2 which were lost to follow-up). Of the 21 who returned compliance data at week 12, 95% (20/21) reporting taking all, or almost all, of prescribed DCA until they advised to stop or completed 12-weeks of treatment. Side-effects were common but typically mild. Common side-effects included nausea and heartburn, and six participants developed some tingling in their fingers which resolved after stopping DCA. Side-effects were more common in those with higher systemic DCA levels. Of those who completed the acceptability questionnaire, 79% (15/19) of participants described the trial as a positive experience. Whilst the study was too small to be statistically significant, at six weeks 79% (19/24) of participants who returned pain scores reported a clinically meaningful reduction in pain scores. Of those who completed all 12 weeks of DCA treatment 75% (15/20) reported clinically meaningful reduction in pain scores. At the end of study, of those who returned painkiller use data, 62% (13/21) reported using less analgesia, and mean Endometriosis Health Profile-30 score improved from 64.7 to 37.0 in the 27/30 participants who returned this data.

The COVID-19 pandemic impacted on the progress of our trial because the study was paused for five months during the recruitment phase. Following resumption of recruitment there was modification in the number of hospital visits.

WHAT IMPACT COULD THE EPiC1 FINDINGS HAVE?

- We have demonstrated we are able to recruit to a study using DCA for endometriosis associated pain, and generated proof-of-concept data that this treatment might reduce pain in patients with superficial peritoneal endometriosis.
- This study has informed the design of and enabled us to secure funding for a double-blind, placebo-controlled feasibility trial (EPiC2; see https://www.ed.ac.uk/centre-reproductive-health/exppect-endometriosis/research/epic2-clinical-trial).
- The aim of the EPiC2 trial is to find out what dose of dichloroacetate has the most impact on painful endometriosis symptoms and has the fewest side-effects. Importantly, the data from EPiC2 will also help plan a future, large scale, UK-wide trial to truly determine whether dichloroacetate can reduce endometriosis-associated pain, improve quality of life and provide value for money.
- DCA could be the first non-hormonal treatment for endometriosis associated pain

HOW WILL THE OUTCOMES BE DISSEMINATED?

The results have already been presented to researchers and clinicians in Edinburgh, and at the following international conferences:

- Society for Endometriosis and Uterine Disorders ASM 2023 (ESPriT1; oral presentation)
- World Congress on Endometriosis 2023 (EPiC1; oral presentation)

Following further analysis, the results will be included in two research papers, one for ESPriT1 and one for EPiC1. The papers will be submitted for scientific publication, with accompanying lay summaries and infographics for public dissemination. The patient panels for each study will support the construction of the summaries.

The outcomes will also be incorporated into future work that will use a Patient and Public Involvement approach to explore precision care of endometriosis from the perspective of people with lived experience of endometriosis.

CONCLUSION

Endometriosis is a common condition associated with debilitating symptoms. Patients with endometriosis want improved evidence to support decision about whether to undergo surgery, and better medical treatments and pain management.

Recruitment to a randomised controlled trial to assess the effectiveness of surgery for endometriosis can be challenging because of preconceived ideas about treatment success amongst patients. However, the ESPriT1 trial showed feasibility of recruitment and has helped to inform the design of (including sample size), and secure funding for, a future definitive multicentre trial.

The EPiC1 trial demonstrated that recruitment and retention to clinical trials of DCA for endometriosis appear feasible. DCA is a promising non hormonal treatment for endometriosis-associated pain but requires assessment in placebo-controlled trials.

RESEARCH TEAM & CONTACT

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Additional Information

Dr Lucy Whitaker completed this Clinical Lectureship and finished her specialist training in Obstetrics and Gynaecology in October 2023. She was appointed Senior Clinical Research Fellow and Honorary Consultant Gynaecologist at the University of Edinburgh in November 2023. She is Chief Investigator of the EPiC2 and ENDOCAN-1 clinical trials, and co-Chief Investigator of the ESPriT2 trial