Preventing recurrence of endometriosis-related pain by means of long-acting progestogen therapy: the PRE-EMPT RCT

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Scientific summary

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Scientific summary

Background

Endometriosis, which affects up to 1 in 10 women, is characterised by the proliferation of endometrial cells outside the uterus, usually within the pelvis. These endometriotic deposits undergo cyclical proliferation in response to ovarian oestrogen, resulting in internal bleeding, scarring and adhesion formation, which causes pain and has a serious impact on quality of life in affected women. Surgical removal or destruction of endometriotic tissue is currently the preferred treatment but the risk of recurrence is high. Recurrence can be controlled by post-surgical hormonal treatment to reduce circulating levels of oestrogen but there is uncertainty as to the clinical and cost-effectiveness of two commonly used modalities: long-acting reversible contraceptive (LARC) and the combined oral contraceptive pill (COCP). Progestogen-based LARCs used in the trial were the levonorgestrel-releasing intrauterine system (LNG-IUS) or depot medroxyprogesterone acetate injection (DMPA).

Objectives

To evaluate the clinical and cost-effectiveness of LARCs compared with COCP in preventing recurrence of endometriosis-related pain and quality of life.

Design

A multicentre, open, randomised trial with parallel economic evaluation. The final design was informed by a pilot study, qualitative exploration of women's lived experience of endometriosis and a pretrial economic model.

Setting

Thirty-four NHS hospitals within the UK.

Participants

Women of reproductive age undergoing laparoscopic surgery for pelvic pain due to endometriosis were eligible if they fulfilled the following criteria:

Inclusion criteria:

- Aged 16–45 years.
- No immediate plans to conceive.
- Scheduled for laparoscopic conservative surgery, or diagnostic laparoscopy with concurrent surgery if endometriosis is found, for pelvic pain associated with endometriosis.
- Willing to be randomised to one long-acting progestogen (LNG-IUS or DMPA) and COCP.

The following women were also eligible if they had recurrent pain and were to have conservative surgery for endometriosis:

- Had one or more previous diagnostic laparoscopies.

- Had previous laparoscopic conservative surgery for endometriosis, provided that this did not involve rectovaginal dissection or bowel resection.
- Used postoperative medical treatment, including the treatment options included in the trial.
- Previous use of treatment options included in the trial as contraceptives.
- Use of preoperative gonadotropin-releasing hormone analogues (GnRHa), provided that this was stopped at least 4 weeks prior to laparoscopy.

Exclusion criteria:

- No endometriosis identified at diagnostic laparoscopy.
- Infertility.
- Any plans for further elective endometriosis surgery (for deep disease or endometrioma).
- Contraindications to the use of hormonal treatment with oestrogen or progestogens.
- Suspicion of malignancy.

Interventions

Four hundred and five women were randomised in a one-to-one ratio via secure internet facility to either LARCs or COCP. The LARC was either 150 mg DMPA or 52 mg LNG-IUS. The COCP formulation contained 30 µg ethinylestradiol and 150 µg levonorgestrel.

The LARC (LNG-IUS or DMPA) was selected before randomisation by the patient if a preference was apparent (or alternatively allocated randomly if there was no opinion).

Outcome measures

Primary outcome

Pain as evaluated by the pain domain of the Endometriosis Health Profile – 30-item (EHP-30) questionnaire at 36 months post randomisation.

Secondary outcomes (evaluated at 6 months, 1, 2 and 3 years):

- The four core domains of the EHP-30 questionnaire (control and powerlessness; emotional well-being; social support; self-image).
- The six modular domains of the EHP-30 (work; relationships with family; sexual relationships; feelings about medical profession; feelings about treatment; feelings about infertility).
- Pelvic pain measured by visual analogue scale (VAS) during periods; during intercourse; at any time.
- Responses to the question 'compared to 1 month ago, would you say your pelvic pain has "Got much better", "Got a little better", "Not changed much", "Got worse"'.
- Fatigue, as measured by Fatigue Severity Scale (FSS) score.
- Menstrual regularity.
- Generic quality of life questionnaire [EuroQol-5 Dimensions, five-level version (EQ-5D-5L)], including index and thermometer scores.
- Capabilities, as a measure of well-being (ICEpop CAPability, ICECAP measure).
- Further therapeutic surgery or second-line treatment for endometriosis as a proxy for recurrence or 'treatment failure', defined as having undergone hysterectomy, surgery for endometriosis, laparoscopy or taking GnRHa treatment.
- Discontinuation rates of randomised treatment (time to first treatment change), with reasons for change.
- Serious adverse events.
- The economic evaluation estimated the cost per quality-adjusted life-years (QALYs) gained.

Sample size

To detect an 8-point difference on the EHP-30 pain domain with 90% power (p = 0.05) and assuming the standard deviation (SD) to be 22 points required 160 participants per group, 320 in total. To account for any loss to follow-up (estimated to be 20%), this target was inflated to 400. Eight points is equivalent to 0.36 SD, which can be considered halfway between a small (0.2 SD) to moderate (0.5 SD) effect size. This size of sample would also give us good power (80%) to detect a 10-point difference in the two stratified analyses of LNG-IUS versus COCP and DMPA versus COCP provided that these subgroups had a roughly even split.

Results

A total of 405 women were allocated to receive either LARC (N = 205) or COCP (N = 200) following laparoscopic surgery for endometriosis. The two randomised groups were comparable in terms of age [29.6 years (6.7 years) vs. 29.3 years (6.6 years)]; body mass index [27.0 kg/m^2 (10.6 kg/m^2) vs. 26.3 kg/m^2 (5.5 kg/m^2)]; early-stage endometriosis: stages I and II (79% vs. 79%); complete surgical excision (92% vs. 90%); white ethnicity (91% vs. 92%) and previous hormonal treatment (27% vs. 23%). Pain scores improved in both groups (24 and 23 points on average) compared with preoperative values but there was no statistically significant difference between LARC and COCP at 3 years [adjusted mean difference: −0.8; 95% confidence interval (CI) −5.7 to 4.2; p = 0.76]. The choice of LARC (LNG-IUS or DMPA) did not alter these findings. Most of the other domains of the EHP-30 were improved in both groups at all time points compared with preoperative scores, with no consistent evidence of any difference between groups when estimates of uncertainty were considered. Women in the LARC group had fewer surgical procedures or second-line treatments compared with those taking COCP (73 vs. 97 events, occurring in 50 vs. 61 women due to repeat interventions), translating to a 33% reduction in time to treatment failure [hazard ratio (HR) 0.67, 95% CI 0.44 to 1.00].

Participants in the LARC group had a slightly higher mean EQ-5D-5L score at 36 months compared with those in the COCP arm (0.693 and 0.686, respectively). The mean adjusted imputed QALY difference between the two arms was 0.043 (95% CI −0.069 to 0.152) in favour of COCP, where participants in LARC group had a lower QALY value than those randomised to COCP (1.937 and 1.976, respectively). Despite this, the COCP group was estimated to be more expensive than the LARC group by £533 (95% CI 52 to 983) per woman over 36 months of follow-up.

Limitations

In the absence of a no-treatment arm, we were unable to demonstrate the effect of surgery alone on preventing recurrence of pain symptoms. While we are able to comment on the effectiveness of a strategy of postoperative prescription of LARC versus COCP, the true impact of these interventions is difficult to gauge as the prolonged duration of follow-up meant that many women had discontinued their allocated treatments. The predominance of white women in the recruited sample limits our ability to be confident about how our results might apply to women from other ethnic backgrounds. Use of telephone follow-up to collect primary outcome data in those who failed to return full questionnaires resulted in missing data for some of the secondary outcomes. While all patients were recruited prior to the COVID-19 pandemic, the number of women who required further surgery may be underestimated, given the negative impact of COVID-19 on waiting lists for elective surgery throughout the UK. It is possible that this may have led to an increase in the use of GnRHa treatment by women who were unable to access surgery for their symptoms.

Conclusions

At 36 months, women allocated to LARCs or COCP had comparable levels of pain, with both groups showing around 40% improvement from presurgical levels. Although COCP is likely to be considered more cost-effective at a threshold of £20,000 per QALY, the difference between the two is marginal. LARCs may be preferred by some women as they are associated with lower rates of surgery, particular hysterectomy and operations for recurrence of endometriosis.

Future work

Future research needs to focus on evaluating newer hormonal preparations, a more holistic approach to symptom suppression and identification of biomarkers to diagnose endometriosis and its recurrence. Active measures need to be adopted to improve the inclusivity of clinical research and ensure that the ethnic mix within participants mirror that of the general population.

Trial registration

This trial is registered as ISRCTN97865475. https://doi.org/10.1186/ISRCTN97865475.

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