Ulipristal acetate versus levonorgestrel-releasing intrauterine system for heavy menstrual bleeding: the UCON randomised controlled trial and mechanism of action study

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Scientific summary

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Scientific summary

Background

Heavy menstrual bleeding (HMB) is the most common gynaecological problem in women of reproductive age, affecting one in four women, and has adverse profound impact on health-related quality of life. Common causes of HMB include structural abnormalities such as uterine fibroids, adenomyosis and dysfunction of the endometrium.

The levonorgestrel-releasing intrauterine system (LNG-IUS) is a proven, effective long-term treatment but about one-third of women cease use by two years due to unpredictable bleeding, hormonal adverse effects or lack of effectiveness. Furthermore, fibroids can make the LNG-IUS less effective. Alternative medical options for HMB exist, but are either less effective or associated with unacceptable adverse effects. Surgical interventions are effective at inducing bleeding control and improving quality of life but are typically incompatible with future fertility. Effective long-term medical treatments for women with HMB are needed.

A class of drugs called selective progesterone receptor modulators (SPRMs) have potential to provide an effective oral treatment for HMB. SPRMs bind with progesterone receptors, resulting in tissue-specific effects in both myometrial and overlying endometrial tissue as well as shrinking uterine fibroids. The SPRM ulipristal acetate (UPA) has been successfully used to treat fibroids, but we do not know how effective UPA is for the treatment of women with HMB who do not have fibroids.

Furthermore, there are uncertainties regarding the mechanism and location of action of UPA, as well as its longer-term safety. SPRMs induce distinctive, non-physiological endometrial changes, which can be confused with endometrial hyperplasia. More recently there has been concern regarding the potential for UPA to cause drug-induced liver injury (DILI). Post marketing surveillance reports resulted in a temporary halt in UPA use in 2018 and 2020. Use of UPA has since been reinstated since January 2021, albeit in a restricted context, reflecting the paucity of existing alternatives for HMB.

Given these uncertainties, we designed the UCON trial to evaluate the safety, tolerability and effectiveness of UPA on HMB and to understand its mechanism of action.

Clinical objectives

Primary objective: to determine whether UPA is more effective at reducing the burden of HMB symptoms than LNG-IUS after 12 months of treatment.

Secondary objectives:

- Ascertain whether UPA use beyond 3 months' and up to 12 months' duration is associated with histological changes to the endometrium and, if so, whether this compromises safety.
- Ascertain whether UPA is more effective than LNG-IUS in relation to menstrual blood loss, sexual activity, generic quality of life, satisfaction with treatment, patient-reported adverse events, and compliance at 3, 6 and 12 months.
- Determine the response to UPA and LNG-IUS treatment difference in the presence of uterine fibroids in terms of (1) alleviation of HMB and (2) change in uterine/fibroid volume.
- Collect data on liver function in women taking UPA, once safety concerns were raised.

Mechanism of action study objectives

To understand how UPA causes a reduction in menstrual bleeding and uterine/fibroid volume in women with HMB, we determined whether UPA administration:

- Alters endometrial cell function (e.g., and not limited to, proliferation, apoptosis, expression of steroid receptors, tumour suppressors and inflammatory mediators).
- Reduces blood plasma flow in the endometrium, uterine myometrium and fibroid tissue.
- Alters the volume fraction of the extracellular matrix in these tissues.
- Reduces uterine and fibroid volume.

Design

This was a randomised, open-label, parallel group, multicentre trial with embedded mechanistic study.

Methods

Setting

The trial recruited participants in 10 sites in NHS hospital settings across the UK between 2015 and 2020. The mechanism of action study was conducted solely at the Edinburgh site.

Participants

For the main trial, informed consent was sought from premenopausal women (aged 18–50 years) with self-reported HMB, no contraindications to LNG-IUS or UPA. Those with uterine size greater than equivalent 14-week size or with submucosal fibroids > 2 cm were excluded. Other exclusion criteria relating to use of other treatments and current health status were applied, including history of severe hepatic impairment.

Screening and randomisation

Participants were recruited in gynaecology clinics by research nurses who screened patient referral letters. Following consent, haemoglobin and circulating estradiol levels were assessed, clinical history elicited and transvaginal and/or abdominal ultrasound and endometrial biopsy were obtained if not previously performed. Following this, and confirmation of eligibility, randomisation was via a web-based central service based at Birmingham Clinical Trials Unit to allocate women in a 1 : 1 ratio using a minimisation algorithm. Screened patients in Edinburgh were offered the opportunity to participate in the mechanistic study.

Interventions and follow-up

Those allocated to UPA received three courses of treatment, each course comprising a daily 5-mg oral dose for 12 weeks followed by a four-week break. Those allocated to the LNG-IUS had it fitted in hospital or primary care. Participants allocated to UPA returned to hospital to collect their repeat prescription at 3 and 6 months, and may have been seen by a member of the care team if required. They were then seen in clinic at 12 months for ultrasound scan (USS) and haemoglobin/serum estradiol measurement. Those allocated to the LNG-IUS group attended USS at 12 months. Follow-up at interim time points was conducted by postal questionnaire. Those partaking in the mechanism of action study underwent magnetic resonance imaging (MRI) following randomisation and at the end of treatment cycles two and three. An additional endometrial biopsy was obtained at the end of treatment cycle two.

Outcome measures

Primary

Condition-specific quality of life score as measured by the menorrhagia multi-attribute scale (MMAS) questionnaire at 12 months. Summary scores range from 0 (worst affected) to 100 (not affected).

Secondary

1. Condition-specific quality of life score as measured by MMAS at 3 and 6 months
2. Menstrual bleeding (pictorial blood loss assessment chart)*
3. Cycle regularity (ordinal four-point scale)*
4. Duration of period (ordinal three option scale)*
5. Pelvic pain during periods, intercourse and at other times (visual analogue scales; 0 = best outcome, 10 = worse outcome)*
6. Uterine fibroid symptom and quality of life instrument (only given to women diagnosed with fibroids)*
7. Sexual function (sexual activity questionnaire)*
8. Generic quality of life (EQ-5D-5L)*
9. Satisfaction with treatment outcome (five-point Likert scale)
10. Participant rating of effect of treatment on HMB over 12 months (four-point Likert scale)
11. Whether participant is willing to recommend the treatment to a friend (yes/no)
12. Surgical intervention
13. Adherence to trial treatments and reasons for changing treatment, as reported by the participant
14. Serious adverse events and reactions
15. Uterine volume, evidence of adenomyosis, presence of fibroids, largest fibroid volume, endometrial thickness, endometrial appearance, evidence of ovarian cysts at 12 months (USS)
16. Endometrial biopsy at 12 months (UPA group only)
17. Liver function tests, from 20 March 2018 every four weeks (UPA group only)
18. Haemoglobin and serum estradiol at 12 months

* assessed at 3, 6 and 12 months

Mechanism of action

A: Effects on cellular markers of endometrial steroid receptors and metabolising enzymes (governing local endometrial steroid [ligand] availability), cell proliferation, cell survival (apoptosis); detection of genes implicated in control of proliferation in endometrium;

B: Effects on uterine/fibroid structure addressed by obtaining volume measurements for the whole uterus, and for the total volume of fibroids when present, by using high resolution structural MRI and stereology; and

C: Uterine vascularity using dynamic contrast-enhanced MRI (DCE-MRI).

Urgent safety measures

In November 2017, the European Medicines Agency (EMA) issued an urgent drug alert for UPA due to a small number of reports of serious liver injury. A detailed investigation by the regulatory authorities was undertaken and it was found that eight reports of serious liver injury were reported in Europe from an estimated 740,000 women using UPA for uterine fibroids. Restrictions on prescribing UPA were subsequently issued and the trial sponsor implemented an urgent safety measure (USM) in February 2018, which halted recruitment. Those allocated UPA were allowed to complete their current course of UPA treatment but not commence any further outstanding courses. In addition, they commenced monthly assessment of LFTs (as well as a post treatment test approximately 2 weeks after the last course of UPA). In August 2018, the halt on UPA prescribing was lifted and recruitment to UCON resumed in October 2018 with additional safety measures in place, including exclusion of those with any history of liver disease [defined as levels of alanine transaminase (ALT) or aspartate aminotransferase (AST) of more than two times the upper limit of normal] and LFT monitoring as described above. UPA was stopped if women had an ALT or AST more than three times the upper limit of normal and a hepatology opinion was sought. In March 2020, the EMA temporarily suspended use of UPA a second time due to ongoing concerns regarding hepatotoxicity and a further USM was issued. All treatment courses of UPA

were immediately stopped. In view of the second USM, the investigators, in discussion with the funder, chose premature closure of recruitment to the study but planned follow-up actions continued as per protocol.

Statistical considerations

The study was powered to detect a clinically useful difference in MMAS score (13 points) between the two groups at twelve months. To detect a difference of this size [0.5 standard deviations (SDs)] with 90% power (p = 0.05) would require 86 women in each group (172 in total). To allow for a 20% loss to follow-up or pregnancy, the sample size was inflated to 220 women. Following the initial USM, this figure was inflated to 302 women to ensure that there were adequate responses in the primary analysis population (defined below) to detect the same size of difference.

The original planned primary analysis population comprised all participants, regardless of adherence to treatment, employing suitable regression models to estimate difference between groups. The enforced non-compliance as a result of the withdrawal of UPA had substantial implications for the validity of the data reported by participants. It was therefore necessary to redefine analysis populations, considering the restrictions that prevented women taking their courses of UPA might influence their responses and any other new potential biases that may be apparent in either group due to, for example, knowledge of the safety concerns around UPA. The primary analysis population would now comprise participants with questionnaire responses received prior to the first USM (12 February 2018), along with questionnaire responses from participants recruited following the study restart (18 October 2018) provided that the responses were returned before the second USM (17 March 2020).

Results

Main trial

A total of 4471 women were approached for the study, with 236 consented and randomised, of whom 181 (77%) returned primary outcome data at 12 months (103 within the primary analysis population). Baseline data were comparable between groups; 92% were white, 34% had fibroids and 8% adenomyosis.

In the primary analysis population, MMAS scores substantially improved in both arms, but at 12 months there was no evidence of a difference between the UPA [median score category: 76–99, IQR (51–75 to 100), n = 53] and LNG-IUS [median score category: 76–99, IQR (51–75 to 100), n = 50] groups (adjusted OR 0.55, 95% CI 0.26 to 1.17; p = 0.12). Rates of amenorrhoea where much higher in those allocated UPA compared with LNG-IUS at each time point (3 months: 56% vs. 5%, adjusted OR 29.3, 95% CI 7.37 to 116; 6 months 53% vs. 10%, adjusted OR 11.7 95% CI 3.78 to 36.0; 12 months: 64% vs. 25%, adjusted OR 7.12, 95% CI 2.29 to 22.2). There was no evidence of a difference in the other patient-reported outcomes although there was considerable uncertainty. In those with uterine fibroids, there were no changes in fibroid or uterine volume in either treatment group at 12 months. On endometrial biopsy, seven participants (8%) had evidence of progesterone receptor modulator associated endometrial changes (PAEC) at 12 months, although none was observed at a further 6 months post treatment; there were no cases of endometrial malignancy. Rates of serious adverse events were low, and no patients required admission to hospital for management of deranged liver function tests due to UPA use.

Mechanism of action study

Effects of UPA administration on the uterus: UPA produced a reduction in cell proliferation in the endometrium, as well as alteration of other local endometrial cellular markers (steroid receptor and steroid metabolising enzyme expression) creating a local endometrial oestrogenic environment. The effects on endometrial cellular markers were reversed upon withdrawal of UPA treatment. Stereological analysis in 19 patients showed that UPA did not produce a reduction in the volume of the uterus, irrespective of coexisting fibroids or adenomyosis. DCE-MRI in 15 patients showed that UPA appears

not to have an effect on uterine blood flow. If adenomyosis was present in the uterus, there was a significant increase in plasma volume in the endometrium. However, one of the five women with adenomyosis also had fibroids.

Effects of UPA administration on uterine fibroids: DCE-MRI studies showed that UPA produced an average reduction in plasma volume in 11 fibroids, which may be interpreted as being due to a reduction in extracellular matrix components. This finding was not supported by stereological analysis, which failed to show a reduction in the total volume of fibroids in eight patients. However, it should be noted that the number of subjects studied is small.

Conclusions

Both UPA and LNG-IUS alleviated the adverse impact of heavy menstrual bleeding on quality of life but we found no evidence of a difference between groups over 12 months. UPA was evidently superior to LNG-IUS in terms of inducing amenorrhoea. We observed no difference in reduction in the volume of the uterus, whether or not fibroids were present and no difference in change in the volume of fibroids was observed.

Analysis of selected markers of endometrial cellular function demonstrated UPA modulation of the progesterone receptor, resulting in molecular and cellular alteration in steroid receptors within the endometrium, consistent with the development of a local (endometrial) oestrogenic microenvironment. Despite this, there is no evidence of pathological endometrial changes. We demonstrated that alteration in the endometrial microenvironment reverses on cessation of UPA treatment, a key factor for a medical treatment of HMB, particularly for those who wish to preserve fertility.

UPA now has restricted availability due to concerns regarding hepatotoxicity. Findings from this study may offer insights into mechanism of action of other SPRM class members. New, effective and acceptable oral medical treatment options are needed to address an important unmet clinical need.

Recommendations for research

1. Further studies of medical treatments for HMB
    a. Developing other SPRMs, not associated with DILI
    b. Other hormonal/non-hormonal medical treatments for HMB
2. Patient populations that encompass both the symptoms of HMB and underlying aetiologies, including structurally normal uterus, adenomyosis and small fibroids
3. Study design with outcome measures impact on menstrual bleeding pattern, pelvic pain and impact on haemoglobin and iron-deficiency, as well as quality of life
4. Qualitative studies to determine what are the most important outcomes to women who suffer HMB

Study registration

This trial is registered as ISRCTN 20426843.

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