# Potential candidate for oral pericoital contraception: evaluating ulipristal acetate plus cyclo-oxygenase-2 inhibitor for ovulation disruption

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## ABSTRACT

**Background** There remains considerable global unmet contraceptive need, with almost 200 million women reporting desire to limit or space childbearing without contraceptive use. Researchers have documented worldwide interest in an oral, on-demand contraceptive option were it available. Candidates for use include ulipristal acetate (UA), levonorgestrel and cyclo-oxygenase-2 (COX-2) inhibitors alone or in combination.

**Methods** We performed an exploratory, prospective study of matched menstrual cycles: one baseline cycle and one treatment cycle of UA 30 mg plus meloxicam 30 mg just prior to ovulation. The primary outcome was ovulation disruption, defined as unruptured dominant follicle for 5 days. Secondary outcomes included comparing cycle length, endometrial stripe thickness, and side effects.

**Results** Nine participants completed all study procedures in both cycles. Ovulatory disruption occurred in 66.7% (n=6) of treatment cycles and all but one demonstrated features of ovulatory dysfunction. Cycle length (mean±SD) was longer in the treatment cycle (31.9±4.0 vs 28.6±3.5 days, p<0.01). Secondary outcomes did not differ between the two cycles.

**Conclusions** UA plus the COX-2 inhibitor meloxicam disrupts ovulation at peak luteal surge and is a promising candidate for evaluation as a pericoital oral contraceptive.

**Trial registration number** NCT03354117.

### Key messages

**What is known on this topic**

⇒ There is popular demand worldwide for an oral, pericoital, on-demand contraceptive option.

⇒ COX-2 inhibitors like meloxicam disrupt ovulation even once the luteal surge has begun, unlike the current emergency contraceptive pills levonorgestrel and ulipristal acetate (UA).

**What this study adds**

⇒ UA plus the COX-2 inhibitor meloxicam disrupts ovulation at peak fertility and may be the best candidate for a pericoital oral contraceptive option.

**How this study might affect research, practice or policy**

⇒ This study suggests further research into the efficacy and side effects of the combination of UA and meloxicam for pericoital contraception is warranted.

## INTRODUCTION

There is considerable global unmet need for contraception[1] and significant interest worldwide in an oral, on-demand contraceptive option. Many women use repeat emergency contraceptive (EC) pills as a primary method, despite limited data on efficacy.[2] The days just prior to ovulation, during the luteal surge, are the most critical for EC as this is when it is most challenging to disrupt ovulation and also when fertilisation is most likely to occur. The evaluation of levonorgestrel (LNG) as a pericoital method has not been convincing as it is not effective once the luteal surge has begun.[3] Direct comparison of LNG EC to ulipristal acetate (UA) demonstrates that UA is able to disrupt ovulation even if given just prior to the luteal surge, unlike LNG.[4] Yet neither disrupts ovulation if given just prior to ovulation, during the

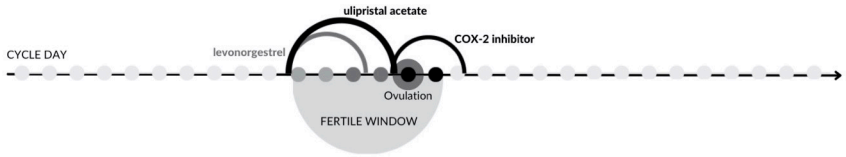


**Figure 1** Efficacy window for oral emergency contraception. This represents a typical 28-day cycle, where the fertile window includes assumptions of intrauterine sperm survival for up to 5 days and oocyte susceptibility for 24 hours after ovulation. The half circles represent previously established time periods of these methods.[5]

luteal surge.[5] Cyclo-oxygenase-2 (COX-2) inhibitors are non-steroidal anti-inflammatory medications that disrupt ovulation by preventing cumulus cell expansion, which occurs after the luteal surge.[6] Indeed, LNG plus a COX-2 inhibitor is more effective than UA alone during the luteal surge.[5] No studies to date have evaluated the addition of COX-2 inhibitors to UA for ovulation disruption.

Our objective was to evaluate UA plus a COX-2 inhibitor on ovulation disruption at peak fertility with the goal of establishing a lead candidate for evaluation as a pericoital oral contraceptive as the combination of these two medications are hypothesised to be effective over the entire fertile window (figure 1).

## METHODS

We conducted a prospective, open-label exploratory pilot study to evaluate the effect of UA plus the COX-2 inhibitor meloxicam on ovulation disruption at the peak of the luteal surge. The study was approved (Stanford Institutional Review Board eProtocol #43881) and registered (clinicaltrials.gov NCT03354117). We aimed to include 10 healthy participants aged 18–35 years with regular menstrual cycles, body mass index (BMI) $\leq$30 kg/m$^2$, no exposure to hormonal medication, without pregnancy or lactation in the prior 3 months, ovulatory baseline cycles, no chronic medical conditions, and who committed to using nonhormonal contraception during the study as needed. Our participant number was a convenience sample based on our anticipated budget and the exploratory nature of the study, as well as the number of participants included in similar studies.[5]

Our study methods (including definitions of lead follicle, luteal surge, and ovulatory progesterone) reflect parameters from published studies of EC efficacy.[5] We followed each participant through two cycles: (1) baseline cycle, to identify normal ovulatory parameters and (2) treatment cycle, administering a one-time dose of two pills: UA 30 mg and meloxicam 30 mg during the fertile window, defined by lead ovarian follicle with mean diameter of 18 mm, again based on prior study protocols.[5] During each cycle, follicular phase evaluation included three times weekly ultrasounds and luteinising hormone (LH) measurements to identify growth of lead follicle and luteal surge. Based on prior studies, we defined the timepoint when the lead follicle reached 18 mm as entering the fertile window. During the fertile window, our protocol changed to daily measurements of follicle size and LH levels to assess for ovulation and peak of luteal surge. Luteal phase measurements included symptom reporting and a progesterone level approximately 7 days after the final daily ultrasound. Based on reported parameters from similar studies, *ovulation disruption* was defined as delayed lead follicle rupture (>5 days) and features of *ovulatory dysfunction* defined based on prior studies (table 1).[5] Features of ovulatory dysfunction included (1) a lead follicle that persists, unruptured, for 5 days after reaching 18 mm in diameter, (2) a blunted LH peak, defined as <15 IU/L and (3) a non-ovulatory luteal phase progesterone level, defined as <3 ng/mL.[5]

All data were collected using REDCap (Research Electronic Data Capture) (Stanford Grant #UL1 TR001085) and coded data were exported to Excel (version 16.31) for analysis. The primary outcome was *ovulation disruption*. Secondary outcomes including cycle length, bleeding pattern, maximum follicle size, and endometrial stripe thickness were compared using paired t-tests.

### Patient and public involvement

This research was developed in response to prior published studies indicating patient interest. We did not involve patients in study design or recruitment. We will disseminate results to all study participants upon publication.

## RESULTS

At our academic institution, we screened 22 individuals for participation and enrolled 14 participants who met the inclusion criteria and completed baseline cycles from May 2018 to March 2019; five participants were ineligible following an abnormal baseline cycle and ovulatory parameters. Nine participants completed both baseline and treatment cycles and were included in the final analysis; mean BMI was 24.5±3.9 kg/m$^2$ with all but one participant with a BMI <25 kg/m$^2$. Mean age was 31.4±4.7 years. We included one participant aged 38 years, which was outside our initial inclusion criteria. This participant was also the only participant with BMI >25 kg/m$^2$ and did not vary in any other baseline characteristics, primary or secondary outcomes and was included in the analysis. All participants analysed demonstrated normal baseline ovulatory function.

**Table 1** Baseline and treatment cycle parameters with ovulation dysfunction criteria

| Cycle 1: Baseline cycle | | | | Cycle 2: Treatment cycle | | | | | | Ovulation dysfunction | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | LF ≥18 mm | | | LF ≥18 mm, day of medication | | | | | Ovulation disruption | | | |
| Subject | Total cycle length (days) | Cycle day | LH level (IU/L) | Total cycle length (days) | Cycle Day | LH level (IU/L) | LF maximum diameter (mm) | Maximum ES thickness (mm) | *Luteal P level (ng/mL) | LF persist ≥5 days | LH surge blunted | *Non-ovulatory luteal P | Met >1 ovulation dysfunction criteria |
| 01 | 27 | 10 | 8.7 | 31 | 10 | 7.2 | 24.2 | 21.6 | 1.3 | Yes | Yes | Yes | Yes |
| 02 | 32 | 12 | 4.4 | 32 | 13 | 18.5 | 22.9 | 11.5 | 5.7 | No | Yes | No | Yes |
| 04 | 29 | 11 | 13.6 | 29 | 10 | 6.2 | 25.7 | 9.30 | 6.6 | Yes | No | No | Yes |
| 05 | 34 | 17 | 34.8 | 37 | 16 | 14.6 | 21.0 | 12.1 | 1.5 | Yes | No | Yes | Yes |
| 06 | 26 | 10 | 13.9 | 28 | 10 | 7.8 | 23.1 | 12.8 | 5.3 | No | No | No | No |
| 07 | 25 | 9 | 5.4 | 34 | 11 | 5.7 | 21.8 | 12.7 | 4 | Yes | Yes | No | Yes |
| 09 | 24 | 9 | 9.7 | 27 | 11 | 7.9 | 23.9 | 9.6 | 8.8 | Yes | Yes | No | Yes |
| 10 | 32 | 14 | 9.8 | 36 | 17 | 10.9 | 18.9 | 12.3 | 3 | Yes | No | No | Yes |
| 12 | 28 | 10 | 55.2 | 31 | 10 | 6.80 | 17.4 | 11.6 | 5.4 | No | Yes | No | Yes |
| Mean | 28.6 | 11 | 17.3 | 31.9 | 12 | 9.5 | 22.1 | 12.6 | 4.6 | | | | |
| SD | 3.5 | 2.7 | 16.8 | 4.0 | 2.7 | 4.4 | 2.6 | 3.6 | 2.4 | | | | |
| Median | 28.0 | 10.0 | 9.8 | 32.0 | 11.0 | 7.8 | 22.9 | 12.1 | 5.3 | | | | |
| Range | 24–34 | 9–17 | 4.4–55.2 | 27–37 | 10–17 | 5.7–18.5 | 17.4–25.7 | 9.3–21.6 | 1.3–8.8 | | | | |

Ovulation dysfunction criteria defined based on established definitions from prior studies.
*Ovulatory luteal phase progesterone level defined as ≥3.[5]
ES, endometrial stripe; LF, lead follicle; LH, luteinizing hormone; P, progesterone; SD, standard deviation.

*Ovulation disruption* was demonstrated in 67.7% (n=6) participants in the treatment cycle. Most (88.9%, n=8) participants met some criteria for *ovulatory dysfunction* (table 1). Significant differences between treatment cycle and baseline included longer cycle length (31.9±4.0 days vs 28.6±3.9 days, p<0.01) and lower progesterone level (4.6±2.4 vs 10.5±3.2 ng/mL, p<0.01). There was no difference in endometrial stripe thickness or maximum follicle size. One participant reported irregular bleeding during the luteal phase in both baseline and treatment cycles. All but one participant did have an ovulatory (≥3 ng/mL) luteal progesterone level, suggesting that ovulation did occur at some point during the cycle.

When examining LH trends around study medication administration we observed that most participants (n=8) received medications during the fertile window, once the luteal surge had begun, and two received medications during the peak of LH surge.

## DISCUSSION

Our results demonstrate that UA plus meloxicam can disrupt ovulation during the luteal surge including during the peak of luteal surge. The addition of meloxicam may increase the efficacy of UA when administered during the peak of luteal surge, when conception risk is highest. This medication combination is an important candidate to evaluate as oral pericoital contraception. When we compare ovulation disruption rates in our study with the previous studies on which our protocol is based, the combination of UA and meloxicam disrupted ovulation at each phase of the fertile window more than any other medication previously studied (figure 2).[5]

Compared with the baseline cycle, treatment cycles were approximately 3 days longer, though there was no difference in endometrial stripe thickness or irregular bleeding. Cycle length changes are an important parameter as people interested in oral, on-demand contraception may also be using fertility awareness methods which can be affected by cycle length changes.

The strengths of this study include a rigorous assessment of ovulation in baseline and treatment cycles. We designed our protocol based on other similar studies of EC efficacy, allowing us to make direct comparisons more appropriately, despite limited resources.[5] We also had excellent study compliance despite the intensive protocol, with nine participants completing all ultrasounds and laboratory testing.

While our study does suggest that the addition of meloxicam to UA may improve efficacy when used during the days just prior to ovulation, it had several limitations. As an exploratory pilot study, it was not powered to demonstrate statistical differences between cycles nor was it able to compare study medication directly to UA alone. Prospectively determining the peak of the luteal phase was challenging with laboratory return times and only two participants received medication at the peak of the luteal surge, as was our intention, with most receiving medication during the luteal surge. With the intricate mechanisms of ovulation disruption there is a question of possible redundancy of UA and COX-2 inhibitor in affecting cumulus expansion, which is induced by gonadotropins and

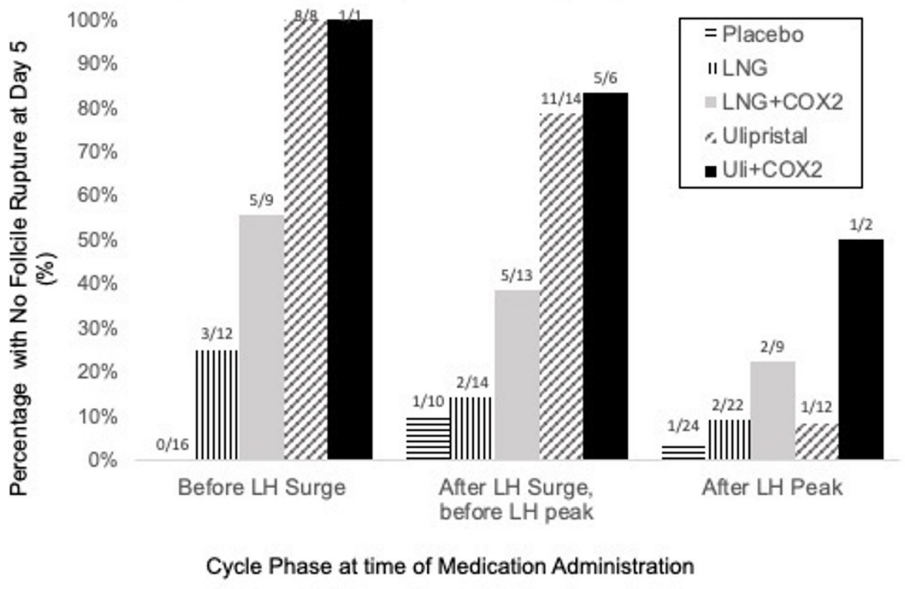


**Figure 2** Percentage of participants with ovulation disruption in treatment cycle, defined as delayed follicle rupture >5 days after receiving study medication. Ulipristal acetate plus COX2 data (in black) from this study, compared directly with data from Table 3 of Brache *et al*.[5] Above each bar line, numbers signify participants with no follicle rupture at day 5 of all the participants who received that medication during that cycle phase (number of participants with disrupted ovulation/total participants). COX2, cyclo-oxygenase inhibitor (meloxicam); LH, luteinising hormone; LNG, levonorgestrel; UA, ulipristal acetate.

mediated by prostaglandins.[6] Finally, true efficacy and side effect measures were beyond the scope of the study and require evaluation with a further study on repeat dosing. For this study we did not measure liver enzyme levels due to single-dose administration of the study medication. Given the potential impact of repeat UA on liver enzymes, this measurement is critical for future studies.[7]

Patients, clinicians and funders are very interested in the development of an effective oral pericoital contraceptive. A viable candidate must be effective during the peak of the luteal surge, when conception risk is highest. Our study demonstrated the biological plausibility of using the novel combination of UA plus meloxicam to disrupt ovulation at this time point. Our study also suggests that the addition of meloxicam to UA use as EC may improve efficacy.

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**Contributors** EPC and PDB conceived the presented idea. EPC developed the theory and performed the computations. KL and KAS verified the analytical methods. All authors discussed the results and contributed to the final manuscript. EPC is the guarantor.

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**Competing interests** None declared.

**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.

**Patient consent for publication** Consent obtained directly from patient(s).

**Ethics approval** This study involved human participants and was approved by Stanford University Institutional Review Board. Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request. All inquiries should be addressed to Dr EP Cahill.

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