RESEARCH PROPOSAL

1. General Information

Title:
NCT03614494
levonorgestrel co-treatment for emergency contraception: randomised controlled trial

Protocol number: PRX 2017-01 (Version 6)
Clinical Trial Registration: ClinicalTrials.gov (Identifier number: NCT03614494)

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2. Background Information

Emergency contraception (EC) is used to prevent unwanted pregnancy after unprotected sexual intercourse (UPSI) or after a recognised contraceptive failure such as condom accidents or missing doses of hormonal contraception. Availability of effective EC methods is very important for reducing the occurrence of unwanted pregnancies in these circumstances.

Oral hormonal EC is the most widely adopted EC method in both Hong Kong and most other countries. The EC method currently available for oral use consists of a single dose of 1.5 mg levonorgestrel (LNG) to be taken within 72 hours of UPSI, or 30 mg ulipristal acetate (UPA) to be taken within 120 hours of UPSI (Glasier et al, 2014; Faculty of Sexual and Reproductive Health, 2017).

Studies have shown that LNG is effective as an EC only when given before, but not after, ovulation (Novikova et al, 2007; Noe et al, 2010). This may be explained by its mechanism of action. LNG prevents pregnancy by blocking or postponing the luteinizing hormone (LH) surge, hence disrupting the ovulatory process; this effect is limited to its administration before the onset of the LH surge, but not when it is taken after the LH surge has commenced, a time when intercourse is most likely to result in pregnancy. The more advanced in the follicular phase that LNG is taken, the lower will be its ability to block ovulation and thus prevent fertilization after UPSI (Croxatto et al, 2004). Once the ovulatory process has been triggered by the LH surge, LNG cannot prevent the follicle from rupturing and releasing the oocyte. It was also shown that LNG has no effect on sperm function, fertilization and implantation (Cameron et al, 2017).

UPA, another selective progesterone receptor modulator, has more recently been introduced as an oral EC. Two randomized controlled trials showed that UPA was as effective as LNG for EC within 72 hours of UPSI (Creinin et al, 2006; Glasier et al, 2010). When the results of the two RCTs were combined in a meta-analysis, UPA has significantly lower failure rate compared to LNG [1.36% (22/1617) vs 2.15% (35/1625), p=0.046] (Glasier et al, 2010). The effectiveness of UPA as EC is maintained up to 120 hours after UPSI, which is currently the licensed indication of UPA. In contrast to LNG which has a limited administration period preceding the onset of the LH surge for it to be effective, it was demonstrated that a single dose of 30 mg UPA administered up till the time immediately before the LH peak could still significantly interfere with follicular rupture (Brache et al, 2010). It was initially postulated in some studies that UPA might also have some concurrent inhibitory effect on embryo implantation based on changes in some molecular and histological parameters induced by UPA, but this was not supported by subsequent in-vitro co-culture experiments. One study in Hong Kong also did not support a significant clinical effect of UPA as EC when administered post-ovulation (Li et al, 2016). Therefore, the journey in search of further improvement in the efficacy of oral EC methods, particularly one with effective post- ovulatory action, still continues.

Prostaglandins are “local hormones” that take part in a number of reproductive processes including ovulation (Duffy, 2015), fertilisation (Sugimoto et al, 2015), tubal function (Wanggren et al, 2006; Wanggren et al, 2008) and embryo implantation (Salleh, 2014). Hence, it is postulated that an inhibitor of the cyclo-oxygenase (COX) enzyme, the key enzyme involved in prostaglandin production, may potentially confer a “contraceptive” effect and may act synergistically with LNG for EC, particularly to target at the post-ovulatory events in addition.

Existing clinical trials which explored the effect of several COX-2 inhibitors on ovulatory function were reviewed in a recent publication (Weiss and Gandhi, 2016); this included six clinical trials exploring the effect of rofecoxib, meloxicam and celecoxib on human ovulatory function. It was suggested that administration of these COX-2 inhibitors in the follicular phase could disrupt or delay follicle rupture, but in most of these studies the drug was administered consecutively for at least 5 days, which would be inconvenient in the context of emergency contraception and compliance may be an issue. Only one study explored the use of a single dose of meloxicam concurrently with LNG 1.5 mg; a trend of increased incidence of unruptured follicles was reported in the LNG plus meloxicam group compared to the LNG plus placebo group, and yet statistical significance was not reached, probably due to the small sample size (n=41). There were little data on the clinical effect of COX inhibitors on post-ovulatory events such as embryo implantation.

Based on the above information, we hypothesize that inhibition of prostaglandin synthesis by a COX inhibitor may confer additional contraceptive action when administered in adjunct to the current LNG regimen, as this may result in disruption of both ovulatory and post-ovulatory events involved in the establishment of conception. Blocking prostaglandin synthesis may retard tubal activities and hence slow down embryo transport, leading to delayed arrival of the embryo to the uterine cavity beyond the implantation window. Furthermore, any negative effect of reduced prostaglandin synthesis on endometrial receptivity may further potentiate its contraceptive action. Hence, it is hoped that COX inhibitor and LNG may act synergistically to achieve an enhanced efficacy for EC.

We choose to investigate the effect of piroxicam, one of the longest-acting COX inhibitor (with half- life over 50 hours) that is commercially available, at a single oral dose of 40 mg. An oral dose of piroxicam up to 40 mg is used pharmacologically for pain relief. Although small clinical studies in women undergoing assisted reproduction treatment showed that a low dosage (10 mg) of piroxicam did not interfere with, or might even enhance, implantation rate (Moon et al, 2004; Firouzabadi et al, 2007; Dal Prato and Borini, 2009; Kumbasar et al, 2017), it is probable that a higher dose may prevent implantation.

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3. Objectives:

Aim: To compare the percentage of pregnancies prevented by LNG co-administered with piroxicam or placebo for oral emergency contraception by a randomised controlled trial.

Hypothesis to be tested: LNG plus piroxicam has higher percentage of pregnancies prevented compared with LNG plus placebo for oral emergency contraception.

4. Study design:

This will be a randomised placebo-controlled double-blind clinical trial. A dedicated research nurse will help coordinate subject recruitment, study administration and follow-up of subjects. Subjects who give written consent to participate in this study shall be randomised to either the piroxicam arm (Treatment group) or placebo arm (Placebo group) in 1:1 ratio according to a computer-generated randomisation list in blocks of 10 in sealed envelopes which are prepared by an independent person. The medication will be prepacked by an authorised third party not directly involved in this study. The subjects, clinicians and research staff will be blinded to the group assignment. The codes for the treatment groups will only be revealed to the investigators after completion of the whole study and statistical analyses. It is anticipated that subject recruitment shall take 20 months; follow-up of the subjects will be completed in 2 months further, and a summary of preliminary results will be available by 24 months.

5. Subject selection and exclusion

5.1 Inclusion criteria

Women attending the Family Planning Association of Hong Kong for oral EC will be recruited if they fulfil the following criteria:

(a) healthy women aged 18 years or above;
(b) requesting emergency contraception within 72 h of a single act of unprotected intercourse in the current menstrual cycle;
(c) having menstrual cycles between 24 and 42 days
(d) willing to abstain from further acts of unprotected intercourse and;
(e) available for follow-up over the next 6 weeks.

5.2 Exclusion criteria

(a) post-abortion or postpartum and period have not yet returned,
(b) being on the following drugs currently: anticoagulants, cyclosporine, tacrolimus, corticosteroids, lithium, serotonin reuptake inhibitors (SSRIs), quinolones
(c) having unprotected intercourse in this cycle more than 72 hours or more than once before attending the clinic,
(d) being found pregnant at the time of presentation,
(e) breastfeeding,
(f) having been sterilized (or partner having been sterilized) or having intrauterine contraceptive device in-situ,
(g) uncertain about the date of the last menstrual period,
(h) having used hormonal contraceptive (including EC pill) in the current or past one cycle, or NSAID in the recent one week,

(i) having history of asthma, urticaria or other allergic reactions to piroxicam, aspirin or other NSAIDs,
(j) having history of ischaemic heart disease, heart failure, hypertension or cerebrovascular disease
(k) having history of peptic ulcer disease and/or gastrointestinal bleeding

The proposed start date of this study is 1 August 2018, and it is anticipated that study recruitment will last for two years.

6. Treatment of subjects

6.1 Baseline assessment:

- The subject will be assessed and counselled for the use of EC by the clinic nurse or doctor as routine. Suitable subjects will be enrolled for the study after informed consent.
- A menstrual history will be taken.
- Pregnancy test will be done; only those tested <u>negative</u> will be recruited into study.
- Blood (5 ml into clotted bottle) will be collected for hormonal assay (LH, oestradiol, progesterone). The serum hormonal levels will be used to estimate the cycle day at the time of presentation in relation to the day of ovulation based on the method described by Novikova et al (2007).

6.2 Treatment:

After counselling and obtaining informed consent, eligible subjects will be randomised to receive one of the two treatment regimens, i.e. Treatment group: a single dose of LNG 1.5 mg and piroxicam 40 mg, or Placebo group : a single dose of LNG 1.5mg and placebo under direct supervision. The subject and the research staff responsible for subject follow-up will be blinded to the treatment arm.

The subjects will be advised not to have further acts of coitus before menstruation returns. They will be given a diary chart to record vaginal spotting and bleeding, possible side effects and further acts of intercourse, if any, and the contraceptive method used.

6.3 Follow-up:

A follow-up appointment will be arranged about 1-2 weeks after the next expected menstruation. Information collected at the follow-up visit will include side effects and vaginal bleeding/spotting marked by the subject on her diary card; time of onset, duration and amount of menstrual bleeding and any further acts of intercourse and the type of contraception used (refer to Appendix 1).

If normal menstrual bleeding has not occurred by that time, a pregnancy test will be carried out, and a positive result denotes treatment failure and the woman will be counselled accordingly. If the woman opts for continuing with pregnancy, she will be referred for antenatal care. An additional research follow-up will be arranged post-delivery to record any antenatal, postnatal and neonatal complications. If the woman opts for terminating the pregnancy, she will be referred to the appropriate services.

7. Study outcomes

Primary outcome measure:

- Fraction of pregnancies prevented (%)
  [(expected pregnancies – observed pregnancies] / expected pregnancies)]
  The number of expected pregnancies will be determined by the Trussell's model (Trussell J et al, Contraception 2003; 67:259-265)

Secondary outcome measures:

- Pregnancy rate (%)
- Change in length (shortening / lengthening) of current cycle (days)
- Adverse effects

The data collection sheet is included in Appendix 1. All the clinical data are part of the usual consultations for EC provision.

8. Assessment of safety

The study medication has been in the market for long time. Being a non-steroidal anti-inflammatory drug (NSAID), it is licensed as an analgesic. Adverse effects are few, and the main side effect is gastrointestinal upset and peptic ulceration. The use of piroxicam for a single dose in this study is not anticipated to be at high risk of causing any significant side effects.

Rarely, piroxicam may lead to potentially fatal skin reactions, e.g. Stevens Johnson Syndrome. Anaphylactic reactions may occur in patients without known hypersensitivity to Piroxicam. Patients with asthma and without known aspirin hypersensitivity will be monitored as signs and symptoms of asthma may occur with the use of Piroxicam. If the above adverse events occur, the subject will be attended by the on-site medical staff and referred to the nearest Accident and Emergency Department.

9. Statistics

9.1 Statistical tests:

- The efficacy-evaluable population will include all women who are enrolled into the study and can be contacted for a follow-up where the outcome data are collected.
- Cases with missing data in a certain parameter will not be analysed for that specific parameter; no data imputation will be instituted.
- The percentage of pregnancies prevented will be compared between groups by χ^2 test.
- Logistic regression model using Firth's bias reduction method will be applied to compare the pregnancy rates between groups. Confidence intervals for regression coefficients will be computed by penalised profile likelihood. This is a statistical method recommended for rare events (Puhr R, Heinze G, Nold M, Lusa L, Geroldinger A. Firth's logistic regression with rare events: accurate effect estimates and predictions? Stat Med 2017; 36(14): 2302-2317).
- The rate of occurrence of menstrual changes will be compared between groups using χ^2 test (for nominal categorical variables) and χ^2 test for trend (for ordinal categorical variables).

- The rate of occurrence of adverse events will be compared between groups by Fisher's exact test as some of the cells may contain an expected frequency of less than 5.
- Continuous variables between the two groups will be compared by Student's t-test.
- Statistical analyses will be performed using SPSS version 28 (IBM Corporation, New York, USA), MedCalc version 20 (MedCalc Software Limited, Ostend, Belgium) and R package "logistf" Version 4.1.2 (http://www.r-project.org).
- P-value <0.05 will be considered as statistically significant.

Two subgroup analyses will be performed. The first subgroup analysis will stratify participants into pre-ovulatory versus post-ovulatory at the time of EC based on blood results of serum oestradiol, progesterone and luteinising hormone level on the day of EC (Li et al, 2016). The second subgroup analysis will stratify participants within versus over the body weight limits recommended for the usual dose of LNG-EC (by the cut-off of body mass index at 26 kg/m2 and that of body weight at 70 kg).

9.2 Sample size estimation:
In a previous study on using LNG for EC within 72 hours of UPSI (Glasier et al, 2010), the fraction of prevented pregnancies was 51.9% based on the Trussell's model. With the assumption that the fraction of prevented pregnancies in the placebo group is around 52%, and the fraction of prevented pregnancies in the treatment group should be at least 10% higher than that in the placebo group for it to be clinically meaningful, a minimum of 384 subjects in each group will be required to demonstrate superiority of the proposed treatment with a power of 80% and type I error of 0.05. Assuming that around 10% of the subjects may default follow-up, we plan to recruit a total of 860 subjects.

No interim analysis is planned as it is anticipated that co-administration of oral piroxicam with LNG will not adversely reduce its EC efficacy.

10. Direct access to source data / documents:

Trial-related monitoring, audits and regulatory inspections are allowed.

11. Quality control and quality assurance

Not applicable

12. Ethics:

Ethics approval will be applied before commencement of study. The study medication has been licensed in Hong Kong as an analgesic. Side effects associated with a single oral dose of piroxicam is expected to be minimal. There should not be any major ethical concern. Clinical trial certificate shall be obtained from the Department of Health, Hong Kong, before the study is commenced.

The study will be conducted in compliance with the protocol of the International Conference on harmonization (ICH) Good Clinical Practice (GCP), as well as applicable local regulatory requirement(s) by the Institutional Review Board (IRB), The University of Hong Kong (HKU) / Hospital Authority Hong Kong West Cluster

(HA-HKWC). Confidentiality of the study subjects will be preserved in accordance to these protocols and regulations.

The patient information sheet will explain the aims of the study, possible adverse effects and confidentiality issues. Informed consent will be obtained before the subjects are recruited into this study. Participation in and withdrawal from the study is voluntary.

13. Data Handling and record keeping

All data will be stored and analysed using SPSS. All the investigators will be responsible for data management including data coding, monitoring and verification.

14. Financing and insurance

Funding will be supported by internal research fund of the Department of Obstetrics and Gynaecology, The University of Hong Kong

15. Publication policy

The findings of this study will be submitted for consideration for publication in peer-reviewed scientific journal.

16. Supplements

Nil