FSRH response to new study by Li *et al.* (2023) Oral emergency contraception with levonorgestrel plus piroxicam: a randomised double-blind placebo-controlled trial 17 August 2023

A study published today in the Lancet reports that a combination of levonorgestrel 1.5mg with piroxicam is more effective for emergency contraception than levonorgestrel 1.5mg alone.

Background

The currently available oral emergency contraception options levonorgestrel 1.5mg (LNG-EC) and ulipristal acetate 30mg (UPA-EC) act to delay ovulation until sperm from unprotected sex that has already taken place are no longer viable, thus preventing fertilisation. There are not significant post-ovulatory contraceptive effects, therefore LNG-EC and UPA-EC can be effective only if taken early enough in the menstrual cycle to delay ovulation.

A previous study[1] indicates that only about half of pregnancies that would have occurred without use of emergency contraception (EC) are prevented by use of LNG-EC. UPA-EC can be effective until closer to the time of ovulation than LNG-EC and appears to be slightly more effective.

FSRH guidelines indicate that the much more effective copper IUD (Cu-IUD) - which acts to prevent both fertilisation and implantation and is effective even if inserted after ovulation - should be considered first line for EC.

The new evidence

A new study[2] has investigated the effect of using the long-acting cyclo-oxygenase (COX) inhibitor piroxicam in addition to LNG-EC. The rationale for this was that that as prostaglandins support ovulation, fertilisation, tubal function and implantation, COX inhibitors (which inhibit prostaglandin production) could act synergistically with LNG-EC to affect ovulation, and could also have post-ovulatory contraceptive effects.

Method The double-blinded study randomised 860 individuals requesting LNG-EC within 72 hours after unprotected intercourse (UPSI) to receive either LNG-EC plus piroxicam 40mg po stat or LNG-EC plus placebo. It is noted that all subjects in fact took their allocated drugs within 35 hours after UPSI. The study subjects were healthy, aged >18 years with a known date of last menstrual period and a relatively regular menstrual cycle. They had no medical contraindications to piroxicam. They had a negative pregnancy test, no additional episodes of UPSI since their previous menstrual period, had not recently used hormonal contraception, oral emergency contraception or an IUD, had not recently had a pregnancy and were not breastfeeding. They agreed to not have further UPSI in the following weeks and to attend for follow up/ pregnancy testing 1-2 weeks after their next expected period.

As many episodes of UPSI for which EC is requested would not result in pregnancy even if EC was not

used, this study estimated the number of pregnancies that *would* have been expected without EC, based on the timing of UPSI in the subjects' menstrual cycles. For each of the study groups, the number of observed pregnancies was compared with the number of expected pregnancies. This established the percentage of pregnancies likely to have been prevented by use of LNG-EC/piroxicam and by LNG-EC alone.

Results It was estimated that without EC, 19 pregnancies would be expected in each group. 7 pregnancies were observed amongst 418 eligible subjects in the LNG-EC/placebo group, and 1 pregnancy in the LNG/piroxicam group of 418 subjects. Thus LNG-EC/placebo prevented 63.4% of expected pregnancies (roughly in line with previous studies) and LNG-EC/piroxicam prevented 94.7% of expected pregnancies. The difference was highly statistically significant ($p<0.0001$), with a risk difference of 31.3%.

The study was, unfortunately, unable to compare effectiveness of use prior to ovulation with use after ovulation as it had intended, because too few individuals agreed to have blood tests. And no comparison could be made between individuals with higher and lower BMI and weights because the number of subjects with BMI >26 or weight >70kg was relatively small. There was no apparent difference between groups in terms of side effects or timing of the subsequent menses.

In summary, in this group of healthy individuals with no medical contraindications to use of piroxicam who took oral EC within 35 hours after a single episode of UPSI and had no subsequent UPSI until pregnancy had been excluded:-

- use of LNG-EC together with piroxicam 40mg prevented significantly more of the expected pregnancies than use of LNG-EC alone
- there was no difference between LNG-EC alone and LNG-EC/piroxicam with regard to reported side effects or timing of subsequent menses

Context and considerations

There are some important considerations when considering these findings:-

- The copper IUD is the most effective method of emergency contraception: very few pregnancies are observed after a copper IUD is inserted in line with guidance after UPSI. There is the significant additional advantage that the copper IUD provides highly effective ongoing contraception (this is not the case for oral EC).
- The subjects in this study do not fully represent the typical population of people that request emergency contraception. This could affect the applicability to the general population of the findings for effectiveness and safety. Ways in which the general population might differ from the study subjects include:-
  - Very often people have had multiple episodes of UPSI prior to and after presenting for emergency contraception (study subjects only had a single episode of UPSI within 72 hours).
  - People may have medical conditions that could affect their eligibility for use of piroxicam, or the risk of adverse effects associated with its use.
- There is not direct study comparison of LNG-EC/piroxicam with ulipristal acetate oral EC (UPA-EC). Most studies do not consider the number of expected pregnancies prevented but rather report the

number of pregnancies observed amongst all subjects (including those whose UPSI was unlikely to have resulted in pregnancy). Thus meaningful comparison of data from different studies is very difficult to make. A previous study suggested that UPA-EC might prevent about 67% of expected pregnancies.[1]

FSRH CEU Conclusion

This is exciting research, with potential implications for beneficial change in this area of practice. The study methodology is sound and the findings are robust and clearly presented. Use of LNG-EC with piroxicam could offer a more effective oral EC option that could be effective much closer to and possibly after the time of ovulation.

The copper IUD is extremely effective for emergency contraception and remains effective after ovulation. Unlike oral EC, it offers ongoing contraception. It is thus recommended first line EC. Not everyone will, however, find an IUD acceptable, and it may not be suitable for some people.

UPA-EC can be effective closer to the time of ovulation than LNG-EC used alone and has a greater chance of being able to prevent an expected pregnancy. Robust comparison of effectiveness cannot be made between the findings from this study for LNG-EC/piroxicam and findings from other studies for UPA-EC, but it is possible that LNG-EC/piroxicam could be more effective than UPA-EC. Additionally, there are circumstances in which UPA-EC is not ideal because commencement of ongoing hormonal contraception has to be delayed after it is taken, because it might be rendered less effective by recent use of a progestogen, or because the person has a medical contraindication to its use. In these settings, LNG-EC/piroxicam could offer an alternative to use of LNG-EC alone.

At present, FSRH CEU guidance regarding emergency contraception remains unchanged. It is anticipated, however, that a Guideline Development Group for update of the FSRH Emergency Contraception Guideline will consider the findings of this study and any other emerging evidence and develop guidance that reflects the potential benefit of LNG-EC/piroxicam compared to LNG-EC alone, but also takes into consideration:-

- Possible adverse health effects of piroxicam. Piroxicam is currently licensed in the UK only at a daily dose of 20mg daily for arthritis/ spondylitis. Some common health conditions contraindicate regular use and there would be considerations for people using other drugs including other non steroidal anti-inflammatory drugs.[3] Medical eligibility criteria would be required to minimise risk of adverse events associated with use of piroxicam, taking into consideration that this would be a single dose rather than regular use, but a higher dose. Use for this indication would be off-label.
- Whether LNG-EC/ piroxicam could be offered in situations that differ from that in the study – for example whether it could be used when there had been several episodes of UPSI in the cycle, or could be used more than once in a cycle.

Further research is welcomed to further inform guidance as this approach to oral EC has potential to offer significant benefit.

References

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