Ulipristal acetate

A new oral emergency contraceptive option

DEBORAH BATESON MA(Oxon), MSc(LSHTM), MB BS
KATHLEEN McNAMEE MB BS, FRACGP, DipVen, GradDipEpiBio, MEpi

Ulipristal acetate is a selective progesterone receptor modulator that is indicated as an emergency contraceptive when administered within 120 hours of unprotected intercourse. It is more efficacious than the levonorgestrel emergency contraception pill but less efficacious than insertion of an emergency copper IUD.

Approximately 200,000 unintended pregnancies occur in Australia annually, with one-third occurring among women using a method of contraception.[1] Emergency contraception is used after an episode of unprotected intercourse, contraceptive failure or sexual assault to reduce the risk of unintended pregnancy. Ulipristal acetate (UPA) as a single 30 mg dose is a safe and effective oral option for emergency contraception. Other emergency contraception methods include the 1.5 mg single-dose levonorgestrel emergency contraception pill (LNG-EC) and insertion of a copper-bearing intrauterine device (Cu-IUD) within five days of unprotected intercourse.

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Clinical Associate Professor Bateson is Medical Director of Family Planning NSW, Sydney; and Clinical Associate Professor in the Discipline of Obstetrics, Gynaecology and Neonatology at The University of Sydney, Sydney, NSW.
Dr McNamee is Medical Director of Family Planning Victoria, Melbourne; and Adjunct Senior Lecturer in the Department of Obstetrics and Gynaecology, Monash University, Melbourne, Vic.

What is ulipristal acetate?

UPA is a selective progesterone receptor modulator. The single 30 mg tablet was first approved for emergency contraception in France in 2009. UPA is now available in 89 countries worldwide. UPA is also used at a 5 mg daily dose for the preoperative treatment of moderate to severe symptoms of uterine fibroids, although it was not available for this indication in Australia at the time of writing.

Understanding UPA's mechanism of action requires an understanding of the hypothalamic–pituitary axis and gamete survival. Ovulation is preceded by a surge in luteinising hormone (LH) from the pituitary gland. Following ovulation, the ovum only survives for up to 24 hours unless fertilised, whereas sperm are viable in the female reproductive tract for up to five to seven days after intercourse.[2] Similarly to LNG-EC, UPA prevents or delays ovulation until sperm are no longer viable. UPA, unlike LNG-EC, is effective at postponing ovulation even when the LH surge has started and ovulation is imminent in 78.6% of cases ($p<0.005$ *vs* LNG-EC and *vs* placebo).[3] It is unlikely that UPA has an anti-implantation effect on the endometrium and it does not act as an abortifacient after implantation has occurred.[4]

A meta-analysis of two large randomised trials comparing pregnancy outcomes between UPA and LNG-EC was published in 2010.[5] This showed significantly fewer pregnancies in the UPA-exposed women compared with the LNG-EC group when the drugs were administered within 24, 72 and 120 hours of unprotected intercourse (Table 1).[5] No pregnancy resulted in around 99% of women who had an emergency Cu-IUD inserted within 120 hours of unprotected intercourse, making it much more effective than either oral method.[6]

Fertilisation is most likely when ovulation occurs within the first two days after unprotected intercourse, but because the timing of ovulation is both variable and difficult to predict accurately, administration of UPA is recommended as soon as possible after unprotected intercourse.[2,7]

Data from the meta-analysis additionally suggest that women

TABLE 1. RESULTS OF META-ANALYSIS OF UPA COMPARED WITH LNG-EC ADMINISTERED WITHIN 24, 72 AND 120 HOURS OF UNPROTECTED INTERCOURSE[5]*

EC timeframe after unprotected intercourse	Ulipristal acetate			Levonorgestrel EC			Odds ratio (95% CI)	P value
	Exposed (n)	Pregnancies (n)	Pregnancy rate (%)	Exposed (n)	Pregnancies (n)	Pregnancy rate (%)		
0 to 24 hours	584	5	0.9	600	15	2.5	0.35 (0.11 to 0.93)	0.035
0 to 72 hours	1617	22	1.4	1625	35	2.2	0.58 (0.33 to 0.99)	0.046
0 to 120 hours	1714	22	1.3	1731	38	2.2	0.55 (0.32 to 0.93)	0.025

Abbreviations: EC = emergency contraception; LNG-EC = levonorgestrel emergency contraception; UPA = ulipristal acetate.

* Adapted from Glasier et al. Lancet 2010; 375: 555-562.[5]

with a body mass index (BMI) over 30 kg/m^2 may be at greater risk of failure with LNG-EC and UPA than women with a BMI less than 25 kg/m^2. The effect was more pronounced for LNG-EC than for UPA.[8] However, current advice states that there is insufficient evidence and that either product is potentially suitable regardless of BMI.[9]

When and in whom is ulipristal used?

The 30 mg UPA tablet is indicated for emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or in cases of actual or potential contraceptive failure, such as a broken condom, missed contraceptive pills or missing IUD threads. It can be used in medically eligible women of any age, including teenagers.

At the time of writing UPA is available in Australia by private prescription as an S4 medication. Since 2015, UPA has become available through pharmacies without the need for a prescription in 25 European countries, including the UK and Switzerland. Australia may follow in the future.

How is ulipristal used and is monitoring required?

Women will need to see their doctor within the appropriate time frame for a prescription for UPA. As LNG-EC has been available at pharmacies without a prescription since 2004, emergency contraception consultations have become infrequent in general practice. The following factors are important to consider when prescribing UPA.

When pregnancy cannot be excluded

A urine pregnancy test may be useful in some circumstances to exclude an existing early pregnancy, although it is important to be aware of the possibility of a false negative result if the test is performed within three weeks of unprotected intercourse. Note that inadvertent use of UPA in pregnancy has not raised safety concerns (see below, 'Contraindications, precautions and medication interactions').

There appears to be no harm from the use of UPA by women who have had additional episodes of unprotected intercourse more than 120 hours earlier in the same menstrual cycle or from repeated use in one menstrual cycle (off-label). However, prescribing doctors need to be aware that the LH peak may already have been reached or implantation may already have occurred, in which case UPA will have no effect on preventing pregnancy.

Expected bleeding and follow-up pregnancy testing

Although there is no indication to routinely advise women to return for a follow-up pregnancy test, they should be advised about expected bleeding patterns after use of emergency contraception. Most women experience bleeding within seven days of their expected next menstrual period. Bleeding may occur on average two days later than expected, with 7% of women experiencing menses more than seven days earlier than expected, 18.5% of women more than seven days later and 4% more than 20 days later.[5] Women need to be advised that bleeding after taking UPA may be related to pregnancy (an implantation bleed; see below 'What are the side effects and risks?'). If the next menstrual period is more than seven days late or is light or unusual in any way then women are advised to seek medical advice for a pregnancy test.[10]

Ongoing contraception

Consideration of ongoing contraception is essential. Women should be made aware of the risk of pregnancy later in the cycle if ovulation is delayed and can be advised to use condoms or abstain from intercourse until the next menstrual period. A disadvantage of UPA emergency contraception compared with LNG-EC is that initiation or restarting a hormonal method of contraception must be delayed for five days.[11] Because UPA's action is related to its highly selective effect on the progesterone receptor, concurrent use of progestogen-containing contraceptives may reduce its effectiveness.[12,13] Additional contraceptive precautions will be required while waiting for the hormonal contraceptive method to become effective. For the same reason, concurrent use of UPA and LNG-EC is not advised within the same cycle.

Sexually transmitted infections

Women requesting emergency contraception may have been exposed to sexually transmitted infections (STIs). A risk assessment should be undertaken to determine whether and when STI testing is required.

TABLE 2. COMPARISON OF THE THREE AVAILABLE METHODS OF EMERGENCY CONTRACEPTION

Characteristic	Levonorgestrel-EC	Ulipristal acetate	Copper-bearing IUD
Effectiveness	Not as effective as UPA or Cu-IUD	Most effective oral EC method	Most effective EC method
	May have reduced efficacy in women with BMI >30 kg/m^2	May have reduced efficacy in women with BMI >30 kg/m^2 (but to lesser extent than LNG-EC)	Not affected by body weight
Access	Available without prescription	Requires prescription	Requires insertion by a trained practitioner
Timeframe after unprotected intercourse	Licensed up to 72 hours Can be used up to 120 hours off licence Limited, if any, efficacy 96–120 hours	Licensed up to 120 hours with no loss of efficacy across 5 days	120 hours with no loss of efficacy across 5 days
Major contraindications and medication interactions	No contraindications other than known pregnancy or allergy/ hypersensitivity Interaction with liver enzyme-inducing medications (advise double dose)	Severe liver disease or severe asthma insufficiently controlled by oral glucocorticoids Allergy/hypersensitivity Interaction with liver enzyme-inducing medications; not recommended (double dose not advised)	Current pelvic infection, distortion of uterine cavity No medication interactions
Potentially affected by diarrhoea or malabsorption	Yes		No
Side effects	Headache, dysmenorrhoea, nausea, vomiting and altered vaginal bleeding pattern		Possible initial altered bleeding pattern and probable ongoing increased menstrual blood loss
	Advise repeat dose if vomiting within 2 hours	Advise repeat dose if vomiting within 3 hours	
Breastfeeding	Evidence suggests can be used safely in breastfeeding women with no need to interrupt breastfeeding	Breastfeeding women are advised to express and discard breast milk for one week after UPA is taken	Safe to use
Ongoing contraception	Women can choose to initiate a hormonal method of contraception immediately using 'quick start'*	Cannot initiate hormonal method of contraception immediately using 'quick start' due to potential drug interactions (a delay of 5 days is advised with use of condoms or abstinence in the interim)*	Provides ongoing effective long-term contraception for up to 10 years

Abbreviations: Cu-IUD = copper-bearing intrauterine device; EC = emergency contraception; LNG-EC = levonorgestrel emergency contraception; UPA = ulipristal acetate.
* 'Quick start' describes starting a hormonal method of contraception immediately at the time of the consultation, even if the woman is beyond days 1 to 5 of the menstrual cycle.

Contraindications, precautions and medication interactions

Contraindications to UPA are few. Those listed in the product information include hypersensitivity to UPA's constituents and known pregnancy (Pregnancy Category D). Although very few pregnancies have been reported in women using UPA and data are limited for the effect on the fetus, international postmarketing surveillance monitoring has not raised safety concerns related to the large volume of tablets sold since 2009.

UPA should be used with caution in women with severe asthma treated with oral glucocorticoids, because of UPA's high affinity for the glucocorticoid receptor. Additionally, as UPA contains lactose, it should not be used by women with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

Ulipristal and breastfeeding

UPA has been detected in breast milk for up to five days after use, and breastfeeding women are advised to express and discard breast milk for one week after administration.[14] Although the product information for LNG-EC lists a precaution for its use during lactation, the amount excreted in breast milk is very low and expert opinion supports its use, which may make it the preferred oral emergency contraception option for breastfeeding women.[10,15]

Liver enzyme medication interactions

UPA is metabolised by the cytochrome P450 liver enzymes. Medications that induce

these enzymes, such as rifampicin and rifabutin, some antiepileptic medications (including carbamazepine and phenytoin), some antiretroviral medications and St John's wort, are likely to reduce the effectiveness of UPA, and an alternative method of emergency contraception is advised.[16] Although a double dose of LNG-EC is recommended to improve its effectiveness for women using liver enzyme-inducing medications, double-dosing is not advised for UPA.[10]

What are the side effects and risks?

UPA is not known to be associated with any reduction in long-term fertility and is not associated with a higher risk of ectopic pregnancy.[17] If a pregnancy occurs when UPA has been taken, as for all pregnancies, its location should be assessed if the woman presents with pelvic pain, vaginal bleeding and a positive pregnancy test.

The risk of hormonal side effects with UPA, including headache, nausea, abdominal pain and dysmenorrhoea, is similar to the risk with LNG-EC, and UPA is generally well tolerated.[5,17] Women should be made aware of the risk of emergency contraception failure.

Conclusions

UPA is a new method of oral emergency contraception that is effective when administered within 120 hours of unprotected intercourse. Women seeking emergency contraception need to be aware of the three available emergency contraception options – LNG-EC, UPA and the Cu-IUD – so that they can make an informed decision about which method best suits their circumstances. The advantages and disadvantages of the three methods are compared in Table 2.

The choice of method will be based on a variety of factors, including effectiveness, medical eligibility, breastfeeding status, timing of intercourse in relation to the last menstrual period and ongoing contraceptive needs, as well as accessibility and cost. Ultimately, a decision to use emergency contraception and which method to choose will depend on the woman's individual circumstances and personal preference. MT

References

A list of references is included in the website version of this article (www.medicinetoday.com.au).

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