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Emergency Contraception*

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Abstract

There have been numerous attempts to control fertility after unprotected sexual intercourse (UPSI). From very bizarre methods like the vaginal application of Coca Cola to the more serious attempts using calcium antagonists influencing fertility parameters in sperm to hormonal methods or intrauterine devices. So far, hormonal methods preventing or delaying ovulation have proved to be the most popular starting with the combination of ethinyl estradiol and levonorgestrel (LNG), known as the **Yuzpe regimen**. The first dose had to be taken within 72 hours of UPSI, a second one 12 hours later. Later on, **LNG alone**, at first in a regimen similar to the Yuzpe method (2×0.75 mg 12 hours apart) showed to be more successful, eventually resulting in the development of a 1.5 mg LNG pill that combined good efficacy with a high ease of use. Several efficacious and easy to use methods for emergency contraception (EC) are available on the market today with the most widely spread being LNG in a single dose of 1.5 mg (given as one tablet of 1.5 mg or 2 tablets of 0.75 mg each) for administration up to 3 days (according to WHO up to 5 days) after UPSI. Its limitations are the non-optimal efficacy which is decreasing the later the drug is taken and the fact that it is only approved for up to 72 hours after UPSI. This regimen has no effect on the endometrium, corpus luteum function and implantation, is not abortive and don't harm the fetus if accidentally taken in early pregnancy. It has no impact on the rate of ectopic pregnancies. It has become the standard method used up to this day in most countries. Since the mid 1970s **copper IUDs** have been used for EC, which show a high efficacy. Their disadvantages lie in the fact that EC is considered an off label use for most IUDs (not for the GynFix copper IUD in the European Union) and that they might not be acceptable for every patient. Furthermore IUD-insertion is an invasive procedure and it is required trained providers and sterilized facilities. **Mifepristone** in the dosages of 10 or 25 mg is used with good results as an emergency contraceptive in China for up to 120 hours after UPSI, but has never received any significant consideration in Western countries. While high doses of mifepristone has an effect on endometrial receptivity and will inhibit ovulation if given in the follicular phase and prevent implantation if given in the early luteal phase, low doses such as 10 mg has no impact on the endometrium. Mifepristone does not increase the rate of ectopic pregnancies. The most recent development is the approval of the **selective progesterone receptor modulator ulipristal acetate (UPA)** in the dosage of 30 mg for EC up to 5 days after UPSI, combining the safe and easy application of the single dose LNG pill with an even higher efficacy. It has shown to be more efficacious than LNG and can be used for up to 120 hours after UPSI; the difference in efficacy is highest for 0–24 hours, followed by 0–72 hours following UPSI. No VTE has been reported following UPA-administration or any progesterone receptor modulator. No effect on endometrium, corpus luteum function and implantation has been observed with doses used for EC. Independent of the substance it should be noted that, if there is a choice, the intake of an oral emergency contraceptive pill should happen as soon as possible after the risk situation. A preexsisting pregnancy must be excluded. Possible contraindications and drug interactions must be considered according to the individual special product informations.

Keywords

emergency contraception, ulipristal acetate, levonorgestrel, mifepristone, ''morning after pill'', postcoital contraception

History

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Introduction

There has been an interest in using synthetic steroids for postcoital contraception for several decades now; a first publication this issue appeared in the International Planned Parenthood Medical Bulletin in 1967. Some substances were analysed with the specific aim of using high doses of estrogen as a treatment [1] (Table 2). The first widely spread method was a five-day treatment of highly dosed estrogen, i. e. diethylstilbestrol (DES) in the USA and ethinyl estradiol in the Netherlands [2,3]. In the

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early 1970s. Albert Yuzpe developed the Yuzpe regimen named after him [4], and in 1975 a method was introduced that used progestin only [5]; the same year saw the launch of a copper IUD as a method of postcoital contraception. At the beginning of the 1980s danazol was examined as one was hoping that it would have fewer side effects than the Yuzpe regimen, but unfortunately, it proved to be ineffective. Therefore the Yuzpe regimen became the standard method of postcoital contraception in many countries in the 1980s. In the years following, interest rose in methods that used progestin only. The Special Program on Human Reproduction (HRP) run by the WHO (in collaboration with the World Bank) conducted a large-scale comparative study between the use of 2×0.75 mg levonorgestrel (LNG) and the Yuzpe regimen and after that began to promote the use of the LNG method [6,7]. More recently progesterone receptor modulators have been developed for emergency contraception (EC) [8].

Currently available are the following methods: the single use of a combination of estrogen and gestagen (ethinyl estradiol together with LNG); the single use of a progestin (LNG); the use of the mifepristone (Mifegyn, Mifeprex) (see Table 1), and the insertion of a copper IUD (for all IUDs its an ''off-label'' insertion, but not for the small GynFix, a copper chain IUD (Contrel/Belgium) in the European Union). In addition to those methods, the substance ulipristal, marketed as ellaOne (30 mg as a single dose), has been available in Europe since October 2009 as a method for postcoital contraception up to five days after unprotected sexual intercourse (UPSI) – this method will be discussed in detail in the following chapter.

A Combination of Ethinyl Estradiol/Levonorgestrel (known as Yuzpe Regimen)

In 1977 Yuzpe and Lancee [9] described a combined method for postcoital contraception consisting of 100 μg ethinylestradiol and 0.5 mg LNG; in this case the first dose is taken within 72 hours after having UPSI, and the second dose 12 hours after the first one. This method was the most common one in the USA for postcoital contraception. The same was true for other countries, as the Yuzpe regimen allows to use conventional oral combination pills together with LNG. In case of UPSI during the second or third week of the menstrual cycle the probability of getting pregnant lies at 8:100. When applying the Yuzpe regimen, only 2 in 100 women became pregnant, corresponding to a risk reduction of 75%. A metaanalysis done by Trussell et al. [10] – analysing eight studies – showed a risk reduction of 74% (95%-CI: 63–79%).

The most important side effects are nausea (50%) and vomiting (20%). So far, no study has examined the impact vomiting might have on contraceptive safety. Some doctors prescribe anti-emetics as a routine or have women take in the hormone dose once more if the vomiting occurs within one to two hours after the first intake. Less frequent are strong vaginal bleeding and breast pain. The next menstruation starts within three weeks after the treatment. For 83% of the women the bleeding started prior to the expected menstruation, and for 8% it started four or even more days after. With consideration of the safety of medical treatment no hints are found that a postcoital application of a combination of estrogen-progestin compounds will cause cardio-vascular side effects [11]. In England an interim analysis done in 1999 showed that the 'morning-after pill' had been given in 4 million cases over a period of 13 years without a significant rise in the risk of deep vein thrombosis in the legs [12]. Therefore there are no absolute contraindications except that of an existing pregnancy. Nevertheless, any individual risk of thrombophilia should be taken into account – if needed, a short-term heparinisation (up to three days) may be suggested. Moreover, there are studies available which show that this type of 'morning-after pill' does not provide a teratogenic risk for the foetus in case the method fails.

Levonorgestrel Method

This method comprises the intake of 0.75 mg LNG within 72 hours after UPSI and twelve hours later. In a large-scale, double blinded trial done by the WHO [12], enrolling 1998 women in 14 countries, the LNG method was compared to the Yuzpe regimen. Among those women using LNG the expected pregnancy rate decreased by 85% (95%-CI: 74–93%). Only 23% of all women in the LNG group complained of nausea, and merely 5.6% of vomiting – in the group using the Yuzpe regimen there were 19%. Both groups saw a decrease in effectiveness regarding the time between the intercourse and the beginning of the treatment within the 72-hour timeframe analysed [6,15]. A single dose of 1.5 mg of LNG was shown to be as effective as the devided doses and with similar rates of side effects [6] Following these studies and until to date, LNG 1.5 mg as a single dose taken as soon as possible and within 72 hours of UPSI has become the recommended regimen for oral EC pill. Although EC with 1.5 mg LNG has contributed to the prevention of unwanted pregnancies, it has limitations in terms of efficacy which drops significantly with the time elapsed since UPSI. Pregnancy rates with LNG EC in the first 24 hours are approximately 1.5%, but increase to 2.6% during the period of 48–72 hours after exposure [16–19]. To increase access and allow use within the time frame when it is most effective LNG emergency contraceptive pills are available over the counter in many countries. If administered at least 2 days prior to the luteinizing hormone (LH) surge, LNG causes either a delay or an inhibition of the LH surge, therefore delays or inhibits ovulation in women [20–23]. However, if given when LH has already started to rise, LNG cannot prevent ovulation [22].

Furthermore LNG in regimen used for EC does not affect endometrial development or progesterone level [22]. Human embryo implantation when studied in vitro is unaffected by LNG [24]. Animal studies confirm that LNG does not affect fertilization or implantation [25,26]. These experimental findings are in line with the clinical data on LNG EC [27].

No increased rate in ectopic pregnancies has been observed [60].

LNG EC would not harm the development of a fetus if used after a contraceptive failure or taken by mistake in early pregnancy.

Zhang and colleagues [59] reported in a cohort study, that the rates of miscarriage and malformations and sex ratio at birth were not statistically significantly different between women who used LNG for EC during their conception cycle and those who did not use any hormonal medications.

Mifepristone

Mifepristone is an anti-gestagen, which was mainly developed to allow medical termination of pregnancies (review Australian Public Assessment Report for Mifepristone) [61]. However, it is suitable to be used as an emergency contraceptive pill, too, as numerous trials have shown. Two randomised trials compared mifepristone, at a dosage of 600 mg, to the Yuzpe regimen [28,29]. Mifepristone showed a contraceptive effect of 100% when taken for postcoital contraception. Another large-scale randomised trial giving 600 mg, 50 mg and 10 mg as single doses within the first five day after UPSI showed that all three ways of treatment reduced the pregnancy rate by 85%; however, the begin of the next menstruation significantly correlated with the dosage: a dose of 600 mg led to a delay of one week in 36%, a dose of

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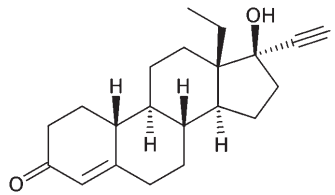
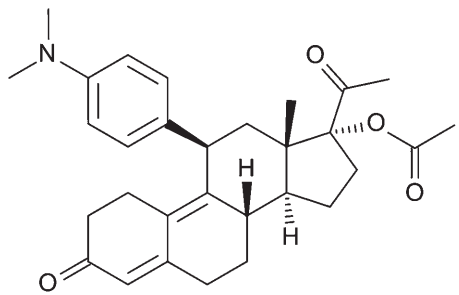
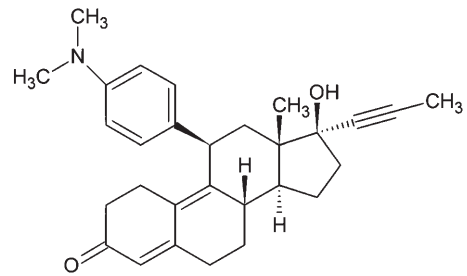
Table 1. Comparison of levonorgestrel, ulipristal acetate, mifepristone for emergency contraception (EC) (UPSI = unprotected sexual intercourse); The Yuzpe regimen as combination of levonorgestrel and ethinylestradiol is mentioned in the following text.

Substance	Levonorgestrel	Ulipristal acetate	Mifepristone
Structure			
Brand names (seletion)	PiDaNa, Plan B, Escapelle	ellaOne	Mifegyne, Mifeprex, Zacafemyl
Half-life (hours)	Terminal: 43 h	32+/−6.3 h	Initial 12–72 h; final 18 h
Peak serum concentration after oral intake	3 h	1 h	1.5 h
Mode of action	Progestagenic	Progesterone receptor modulator	Antiprogestin
Dosage for EC	1.5 mg oral up to 3 (5) days after UPSI	30 mg postcoital up to 5 days after UPSI	10 and 25 mg up to 5 days after UPSI
Contraceptive failure rate (as EC)	About 3.0%	About 1.5% (see Table 4 and Figure 7)	About 1.5%
Registered use	Worldwide	Worldwide 48 countries	Only in China
Hepatic enzyme	Inducer of CYP3A4	Mainly metabolised by CYP3A4, and to a small extent by CYP1A2 and CYP2D6.	Mainly metabolised by CYP3A4
Endometrium effects	No effect	No effect, when used in early luteal phase	Inhibition of endometrial receptivity and implantation when given 200 mg oral at LH +2, **)
Luteal phase effects	No effect when used in early luteal phase	No effect when used in early luteal phase	Doses >50 mg, given in the mid and late luteal phases inhibit corpus luteum, but are not sufficiently effective to prevent pregnancy
Risk of venous thromboembolism	Yes (according package insert - information varies by country) WH0: no relevant risk	No VTE observed in the first 400 000 cases of use	No data available
Comments	No prescription necessary in most countries	Prescription necessary	Prescription necessary in China

*Gemzell-Danielsson et al., 2004.
**Gemzell Danielsson et al., 1993; Hapangama et al., 2001; see review Gemzell & Marions, 2004.
***for 200 mg (Gemzell, 1993).

Table 2. Comparison of different methods for postcoital contraception. According to [8,12–14].

Treatment	First use after unprotected Intercourse (time)	Availability	Effectiveness	Data backup	Notes
High dosage of estrogen (daily 5 mg ethinyl estradiol over 5 days)	0–72 h	Used to be approved for the Netherlands; otherwise, only little use	75%	Randomised trial enrolling 250 women	Obsolete!! High risk of VTE! Ectopic pregnancies
Mifepristone (10 or 25 mg with 25 mg being more effective (Cochrane review by Cheng et al. [13])	0–120 h	Used in China for postcoital contraception; off-label available in several countries	>95%	3 randomised trials with >2300 women	Not available for postcoital contraception in Europe
Estrogen/progestin combination (100 mg ethinyl estradiol and 0.5 mg levonorgestrel as 2 doses 12 h apart)	0–72 h	Since 1980 approved in some countries (e. g. Britain, the Netherlands); unlicensed available as a combination of several oral combination pills	75%	Meta-analysis of 10 trials and >5000 women	Available, but off-label
Levonorgestrel (0.75 mg in 2 doses taken 12 h apart)	0–72 h	Approved in East Europe and Asia	75–85%	3 trials enrolling > 3300 women	
Levonorgestrel (1.5 mg as a single dose)	0–72 h (according WHO: up to 120 h)	Available worldwide	52–85%		Standard method for postcoital contraception
Ulipristal (30 mg as a single dose)	0–120 h	Available in > 40 countries	>85% Superior to Levonorgestrel	2 randomised trials with 3368 women	Launch in European market in 10/2009
Copper IUD	0–120 h after the earliest calculated day of ovulation	Available worldwide, but not approved for postcoital contraception	99.0%	Meta-analysis of 20 trials and >8000 women	Available, but off-label (only GyneFix copper chain IUD registered in the EU for EC)

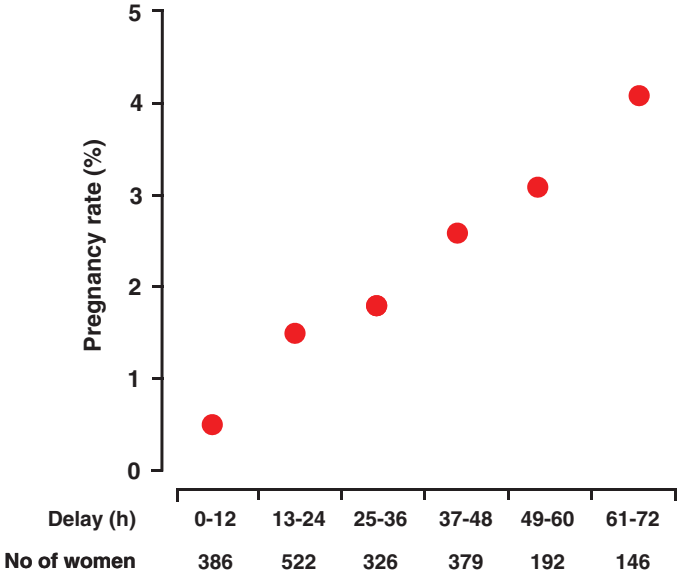


Figure 1. Pregnancy rate by time after unprotected intercourse in women using the Yuzpe method and levonorgestrel as emergency contraception [18].

50 mg to a delay in 23%, and a dose of less than 10 mg only to a delay in 18% of the cases. Mifepristone in doses of 10 or 25 mg are available for EC in China. The effect of mifepristone is well known to be depending on time of treatment during the menstrual cycle and the dose given. A variety of regimens with a single dose as low as 10 mg have been shown to interrupt follicle development thus delay or inhibit ovulation [22,30–32]. While higher doses affect endometrial receptivity and prevents implantation [24,33–35] 10 mg mifepristone has little or no effect on the endometrium [22].

Ulipristal – A Progesterone Receptor Modulator Substance

Ulipristal acetate (UPA) is the first selective progesterone receptor modulator (SPRM) approved for EC (Figure 1). Thus it belongs to the large group of progesterone receptor ligands whose effects stretch from one end of the range, i.e. acting as pure agonists (i. e. progesterone itself) to the other extreme, i. e. that of pure progesterone antagonists. Selective progesterone receptor modulators (SPRM) are located quite in the centre of the range as they feature both agonistic and antagonistic qualities.

Development

UPA was developed by HRA Pharma in collaboration with the US National Institute of Health in Bethesda, Maryland. The time to develop the compound was nearly ten years from the early experimental stage to the Phase III clinical trials. In the mid of 2009 UPA was granted marketing authorisation for Europe by the EMEA. The indication is the one for EC up to 120 hours (5 days) after UPSI or contraceptive failure.

Studies of Receptor Binding

In vitro, UPA competitively binds to the progesterone receptor, the glucocorticoid receptor and the androgen receptor. Simultaneously, it shows only a low affinity to estrogen receptor or mineralocorticoid receptor. In addition to that, UPA also shows a high affinity to the glucocorticoid receptor; in vitro anti-glucocorticoid effects were shown when tested on animals. However, no such effects were observed on humans even after repeated intake of a daily dose of 10 mg. UPA has only a minimum affinity to the androgen receptor and no affinity to the human estrogen receptor or mineralocorticoid receptor.

Pharmacokinetics

The half-life after oral intake is 32 hours. Ulipristal binds up to 97–99.5% to plasma proteins in the blood, and it is mainly metabolised by the cytochrome P450 (CYP3A4).

Mechanism of action

Inhibition of ovulation

UPA is a synthetic progesterone receptor modulator with oral effect which relies on a high binding affinity at the human progesterone receptor. The main mechanism consists of blocking or delaying ovulation. Clinical trials have shown that UPA depending on its dose (10–100 mg), delays the growth of the leading follicle (Graafian follicle) in the mid of the follicular phase. As a result, this leads to a delay in ovulation which was most significant in the highest doses used (50 and 100 mg micronized). This allows UPA to be effective even when administered immediately before ovulation when LH has already started to rise, a time when use of LNG or Yuzpe is too late for ovulation inhibition. In a study comparing early luteal phase treatment with placebo, 10, 50 or 100 mg unmicronized UPA a significant delay in endometrial maturation was seen in the 50 and 100 mg groups compared to the placebo and the 10 mg group upon biopsy four to six days after ovulation [36]. Treatment with UPA resulted in a significant dose-dependent decrease in endometrial thickness as well as an increase in glandular P receptors. Yet, in the doses relevant for EC use (30 mg) UPA has no significant effect on the endometrium.

Comparison the mode of action of LNG with UPA in clinical studies

Three studies investigated the mechanism of action of levonogestrel and UPA for EC:

(1) According to Croxatto et al. [41] and Massai et al. [40] using UPA there is a significant higher number of cycles with with no follicle rupture within 5 days after treatment (administered with a follicular diameter of $\geq$18 mm) using UPA (Figure 3).
(2) Brache et al. [42] showed that UPA caused a delay of preovulatory LH by 4 days (Figure 4) and a high proportion of women (59%) without follicle rupture within 5 days after treatment in a small group of subjects and in only a single trial. LNG is not effective to suppress a beginning LH-surge.

If this phenomenon is drug or dose-related cannot be decided, because studies with higher LNG-dosages are missing. Due to the fact that the LH-surge is a rapid release of prestored LH from pituitary vesicles the UPA should interact with the pituitary LH release from its vesicles. Further studies must show if these vesicles bear progesterone receptors and exocytosis can be blocked by PRMs.

A summary of the mode of action is given in Figure 2.

Endometrium and implantation

In a recent review Gemzell-Danielsson et al. [64] analysed the mechanism of action of ECs. Based on their clinical data and in vitro experiments the authors showed that there is no significant effect on the endometrial development with low dose mifepristone. Although 10 mg of mifepristone may have some minor

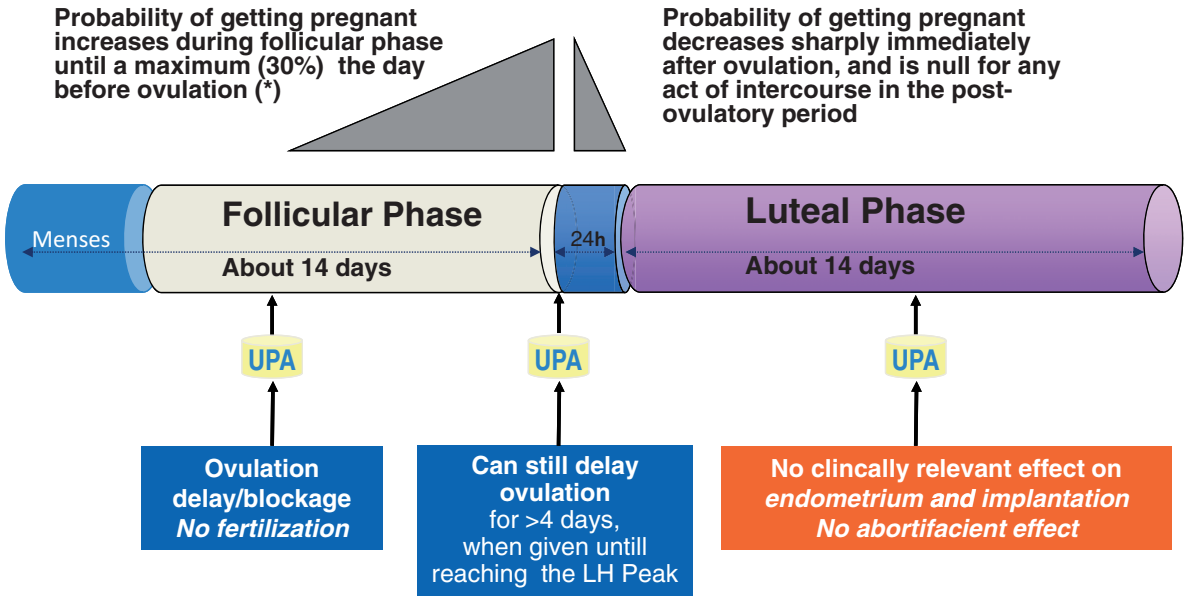


Figure 2. Ulipristal acetate (UPA) (30 mg) for emergency contraception: mechanism of action [39].*

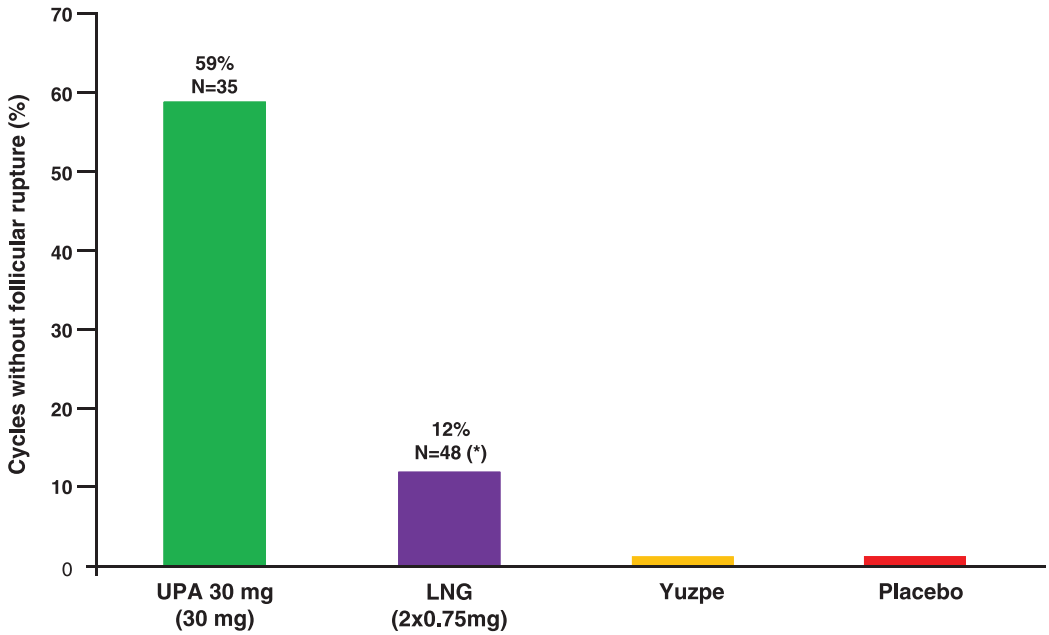


Figure 3. Cycles with no follicle rupture within 5 days after treatment (administered with a follicular diameter of ≥18 mm) [40,41] (with permission).

effects on expression of progesterone receptors or local factors this did not impair endometrial receptivity or embryo implantation. This could also be applied for UPA [64]. UPA caused a significant dose-dependent decrease in endometrial thickness, an increase in glandular P receptors, and a decrease in peripheral node addressins in a dose dependent way similar to that seen for mifepristone Stratton et al. [65,66]. Thus low dose UPA (30 mg) as used for EC has no significant effect on endometrial receptivity and implantation [67].

In contrast UPA (5 mg daily, orally) used for treatment of leiomyoma is causing endometrial changes known as PAEC Mutter et al. [68], Rabe et al. [69] observed for all PRMs during chronical use, a phenomenon not occurring after application of a single dosage. In patients using 5 mg UPA for 3 month as a treatment for leiomyoma three pregnancies occurred. If PAEC changes occur with this treatment, they do not seem to prevent implantation.

Drug safety

Preclincal studies

Preclinical Data on Safety

Based on the conventional studies on safety pharmacology, toxicity in case of repeated intake and genotoxicity, the preclinical data do not reveal any particular harm for human beings. Most of the effects discovered in the general toxicity studies could be related to the mechanism as a modulator to the progesterone receptor and the glucocorticoid receptor. Anti-progesterone effects occurred at an exposition comparable to that of a therapeutic treatment.

Genotoxicity (EMA: CHMP assessment report for ellaOne [62]:

No genotoxic potential.

Reproductive and developmental studies performed with UPA (EMA: CHMP assessment report for ellaOne [62]:
''Ulipristal acetate has no effect on male fertility.

As expected, UPA is embryotoxic at low doses, when given to rats and rabbits in repeated doses at gestation days 6–17 or 6–18 respectively. Considering the pharmacodynamics of the product and the indication applied for, the most important effects to consider are those in live foetuses, and the applicant has chosen a dose in the embryo/foetal studies that allows sufficient foetuses to survive for examination. In rats and rabbits, no effects in live foetuses were observed at doses up to 1 mg/kg/day in the pivotal studies.''

Comment: At doses, which were low enough to maintain gestation in the animal species no teratogenic potential was observed. The safety for a human embryo is unknown, but no safety signal has been noticed from use of the product for EC [71].

Clinical safety data on embryotoxicity and pregnancy (Figure 6).

Two subsets of data are available:
A: Clinical data ($n = 92$) with 82 available outcome (until 12/2012)
B: PV Data until may 2011 (overall $n = 74$; available outcomes $n = 28$).

In these data sets the incidence of spontaneous miscarriages war 18.3% (A) or 7.1% (B). An elective termination of pregnancy was performed in 73.2% (A) and 78.6% (B). Live birth occurred in 8.5% (A) and 14.3% (B). No ectopic pregnancies were reported.

Clincal studies on drug safety

Side Effects

The frequency of side effects after taking 30 mg UPA is comparable to that of taking 1.5 mg LNG. Both forms of treatment show comparable side effects. (Figure 5).

Prevention and management of nausea and vomiting with EC is analysed in a systematic review by Rodriguez et al. [44].

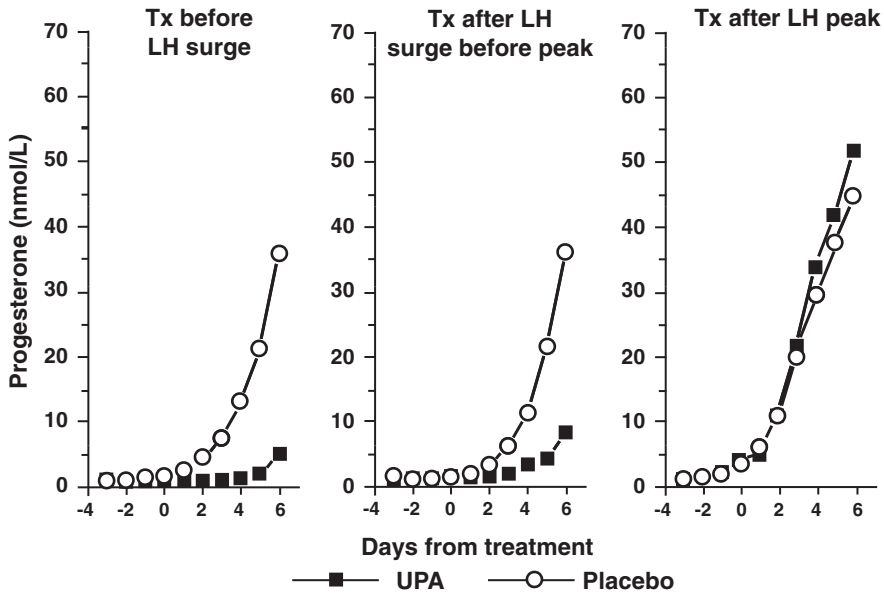


Figure 4. Delay of midcycle rise of luteal progesterone after administration of 30 mg ulipristal acetate: a delay of the onset of progesterone rise of 4 days can be observed in both groups. Mod. from [42]. Reprint with permission from Oxford University Press. Tx = treatment.

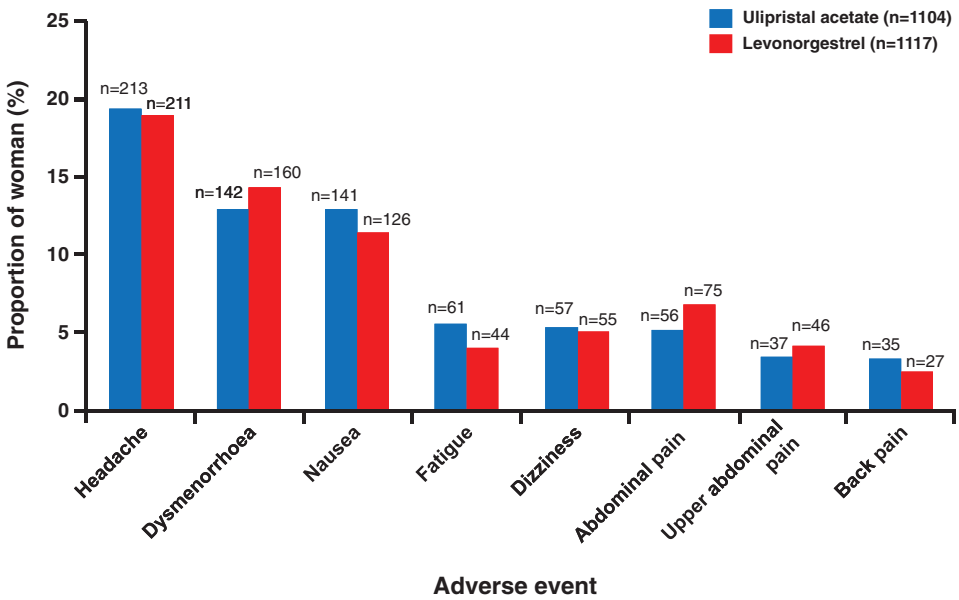


Figure 5. Side effects of ulipristal acetate 30 mg compared to Levonorgestrel 1.5 mg as a single dose. Mod. from [37]. (Reprint with permission from The Lancet Publishing Group).

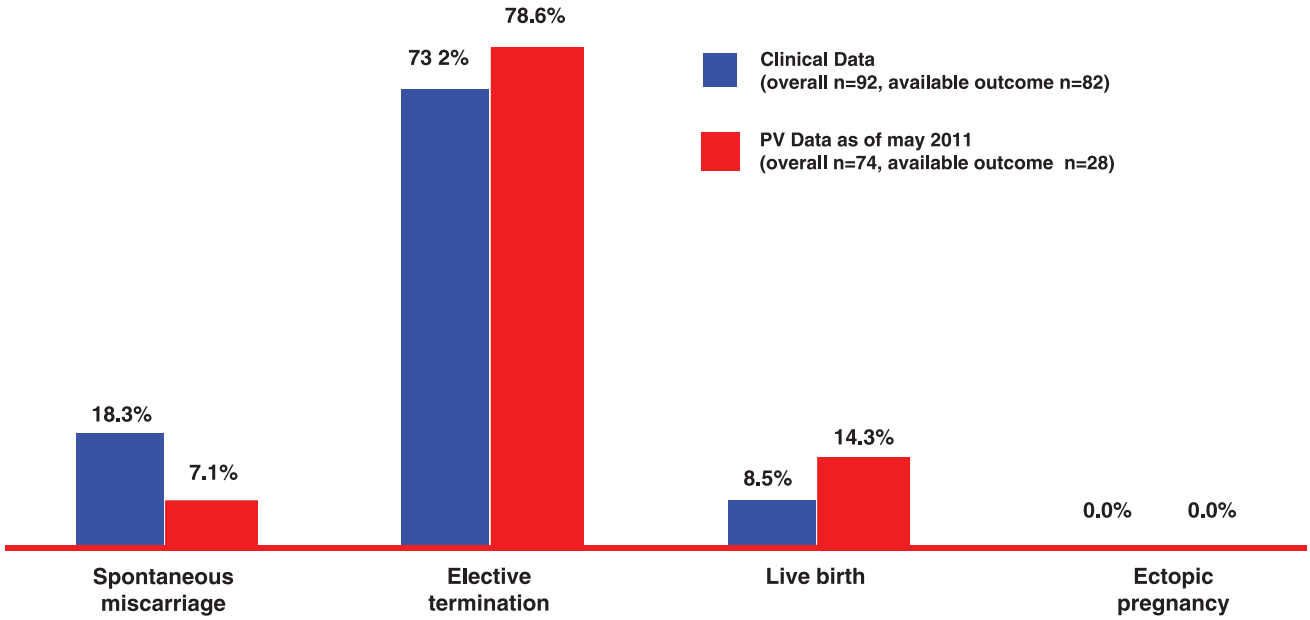


Figure 6. Pregnancies under emergency contraception with ulipristal acetate: Clinical trials & post-marketing data (according to [43]).

Table 3. Comparison of the different study design of clinical trials analysing the contraceptive efficacy of ulipristal acetate (UPA) partially versus levonorgestrel (LNG) for contraceptive use after unprotected intercourse.

Autor/Year	Creinin et al. [37]	Fine et al. [38]	Glasier et al. [14]	Glasier et al. [14]
Study	Randomised Study Monocentric Double blind	Observational study Multicentric family planning clinics	Randomised Study Multicentric family planning clinics	Metaanalysis of [14,37]
Dosage	UPA 50 mg ($n = 775$) 2×0.75 mg LNG ($n = 774$)	UPA 30 mg ($n = 1241$)	UPA 30 mg ($n = 1104$) LNG 1.5 mg ($n = 1117$)	
Study group	Healthy women	Women above 18 years with regular menstrual cycle 48–120 hours postcoital	Women with regular menstrual cycle Until 5 days postcoital	
Comments	Until 72 h postcoital			Rather a pooled data analysis than a meta analysis with combining two different studies

Table 4. Contraceptive efficacy of various emergency contraception methods.

		Yuzpe	LNG					UPA			
Days pc	Hours pc	Lancet [70]	Lancet [70]	Creinin et al. [37]	Fine et al. [38]	Glasier et al. [14]	Meta-analysis* [14]	Creinin et al. [37]	Fine et al. [38]	Glasier et al. 2010 [14]	Meta-analysis* [14]
<1	0–24	2.00% 9/459	0.40% 2/450	1.50% 4/263	n.a.	3.00% 10/337	2.50% 15/600	0.00% 0/273	n.a.	1.60% 5/312	0.90% 5/584
2	25–48	4.10% 15/370	1.20% 4/338	1.00% 3/298	n.a.	2.20% 7/319	10/617	2.20% 6/268	n.a.	2.10% 7/329	2.20% 13/597
3	49–72	4.70% 7/150	2.70% 5/187	2.80% 6/213	n.a.	2.60% 5/196	11/409	0.40% 1/234	2.30% 16/693	1.50% 3/203	0.90% 4/437
4	73–96	n.a.	n.a.	n.a.	n.a.	2.70% 2/73	2/73	n.a.	2.10% 8/390	0.00% 0/63	0.00% 0/63
5	97–120	n.a.	n.a.	n.a.	n.a.	3.00% 1/33	1/33	n.a.	1.30% 2/158	0.00% 0/34	0.00% 0/34
<3	0–72	3.20% 31/979	1.10% 11/976	1.70% 13/774	n.a.	2.60% 22/852	2.20% 35/1625	0.90% 7/775	n.a.	1.80% 15/844	1.40% 22/1617
3–5	49–120	n.a.	n.a.	n.a.	n.a.	8/515	14/515	n.a.	2.10% 26/1242		
0–5	0–120	n.a.	n.a.	13/742	n.a.	2.60% 25/958	2.20% 38/1731	7/775	n.a.	1.60% 15/941	1.30% 22/1714
4–5	73–120	n.a.	n.a.	n.a.	n.a.	2.80% 3/106	2.80% 3/106		1.70% 10/548	0.00% 0/97	0.00% 0/97

Summary of Clinical Data on the contraceptive efficacy of LNG and UPA

Overview about clinical trials analysing the contraceptive efficacy of the Yuzpe method, LNG and UPA for EC (see Table 3 and 4).

Yuzpe and LNG-method. In the original study of Piaggio et al. [18] no difference has been seen between the Yuzpe and the LNG-method (2×750 mg in a 12 hour time difference) and the pooled data analysis showe a decline of contraceptive efficacy linear by time elapsed after UPSI (Figure 1), with has no been verified by later studies such as [14,37]. Whereas Creinin et al. [37] showed lowest pregnancies values (1.0%) after 25–28 hours and a highest rate after 49–72 hours (2.8%) Glasier could not see a change over time up to 5 days (Table 4).

Three studies analysed the effect of postcoital LNG and UPA administration after UPSI:

– Creinin et al. [37] compared the efficacy and adverse effects of UPA to LNG for EC in randomized, double blinded noninferiority trial, enrolling healthy women seeking EC within 72 hours of UPSI. Participants were randomly assigned to receive a single dose of 50 mg of UPA, plus a placebo 12 hours later or two doses of 0.75 mg of LNG taken 12 hours apart. Follow-up was scheduled 5 to 7 days after the expected onset of the next menstrual period. Daily diaries were used from the time of EC use until next menses to record adverse effects and sexual activity.

Results: Contraceptive efficacy was evaluable in 775 of UPA users and 774 of LNG users. Pregnancies occurred in 7 (0.9%, 0.2–1.6%) and 13 (1.7%, 0.8–2.6%) women, respectively. Based on the estimated cycle day of UPSI, 85% and 69% of anticipated pregnancies, respectively, were averted.

Conclusion: UPA is at least as effective as LNG in preventing pregnancies after UPSI and has a similar side effect profile (level of evidence: I).

– Fine et al. [38] evaluated the efficacy and safety of UPA as EC in women presenting 48–120 hours after receiving UPA for UPSI. Women aged 18 years or older with **regular cycles** who presented for EC **48 to 120 hours after UPSI** were enrolled in 45 Planned Parenthood clinics and treated with a single dose of 30 mg UPA. Pregnancy status was determined by high-sensitivity urinary human chorionic gonadotropin testing and return of menses.

Results: A total of 1241 women were evaluated for efficacy. Twenty-six were pregnant at follow-up, for a pregnancy rate of 2.1% (95% confidence interval 1.4–3.1%). These results satisfy the protocol-defined statistical criteria for success because the pregnancy rate was lower than both the estimated expected pregnancy rate and a predefined clinical irrelevance threshold. In addition, efficacy did not decrease over time: pregnancy rates were 2.3% (1.4–3.8%), 2.1% (1.0–4.1%), and 1.3% (0.1–4.8%) for intervals of 48 to 72 hours, more than 72 to 96 hours, and more than 96 to 120 hours, respectively. Adverse events were mainly mild or moderate, the most frequent being headache, nausea, and abdominal pain. Cycle length increased a mean of 2.8 days, whereas the duration of menstrual bleeding did not change.

Conclusion: UPA is effective and well-tolerated for EC 48–120 hours after UPSI (level of evidence II).

– Glasier et al. [14] compared the efficacy and safety of UPA with LNG for EC.

Methods: Women with **regular menstrual cycles** who presented to a participating family planning clinic requesting EC within 5 days of UPSI were eligible for enrolment in this randomised, multicentre, non-inferiority trial. 2221 women were randomly assigned to receive a single, supervised dose of 30 mg UPA ($n = 1104$) or 1.5 mg LNG ($n = 1117$) orally. Follow-up was done 5–7 days after expected onset of next menses. The primary endpoint was pregnancy rate in women who received EC within 72 h of UPSI, with a non-inferiority margin of 1% point difference between groups (limit of 1.6 for odds ratio). Analysis was done on the efficacy-evaluable population, which excluded women lost to follow-up, those aged over 35 years, women with unknown follow-up pregnancy status, and those who had re-enrolled in the study. Additionally, we undertook a meta-analysis of our trial and an earlier study to assess the efficacy of UPA compared with LNG.

Results: in the efficacy-evaluable population, 1696 women received EC within 72 h of UPSI (UPA, $n = 844$; LNG, $n = 852$). There were 15 pregnancies in the UPA group (1.8%, 95% CI 1.0–3.0) and 22 in the LNG group (2.6%, 1.7–3.9; odds ratio [OR] 0.68, 95% CI 0.35–1.31). In 203 women who received EC between 72 h and 120 h after UPSI, there were three pregnancies, all of which were in the LNG group.

In the **meta-analysis** (0–72 h), there were 22 (1.4%) pregnancies in 1617 women in the UPA group and 35 (2.2%) in 1625 women in the LNG group (OR 0.58, 0.33–0.99; $p = 0.046$).

Conclusion: UPA provides women and health-care providers with an effective alternative for EC that can be used up to 5 days after UPSI.

Analysis of the complete study data

Even if the complete data set of [14,37] shows only a trend in favour for UPA versus LNG, the pooled data analysis (called metaanalysis) [14] pooled with [37] shows a significant odds ratio (UPA/LNG) in favour of UPA compared to LNG (Table 4).

Contraceptive efficacy by time after UPSI (Table 4):

LNG: Slight increase up to 2.80% during 49–72 hours in [37], whereas no change over up to 5 days in [14], with low number of subjects in the time window 73–96 and 97–120 hours.

UPA: In [37] study no pregnancy within 0–24 hours, 2.2% within 25–48 and 0.4% within 49–72 hours. No data above 72 hours. Fine et al. [38] starting after 72 hours, showed a decline in pregnancy rate from 2.3% (49–72 hours), over 2.1% (73–96 hours) to 1.3% (97–120 hours) with decreasing number of subjects; no data if the difference is of statistical relevance.

In [14] trial. there are no real difference within the first 72 hours, but no pregnancy occurred thereafter. After 72 hours the groups are small and there might be a selection bias for recruitment of subjects after 72 hours.

Due to the fact, that the metaanalysis of Glasier is in reality a combined data analysis of two different studies (even if 50 mg UPA equals 30 mg micronized UPA) (different selection criteria of subjects - see table) the final results must be interpreted with caution.

Analysis of subsets of data (Table 4)

Two clinical trials (Phase II: 50 mg unmicronized UPA versus 1.5 mg LNG as a single dose [37]; Phase III: 30 mg micronized ulipristal versus 1.5 mg LNG [14] saw the examination of women who used EC between 0 and 72 hours or 0 and 120 hours after UPSI or contraceptive failure. The results of both trials showed that UPA was not inferior for the purpose of EC compared to LNG. The third trial [38] revealed pregnancy rates of 2.1% for UPA versus the expected pregnancies of 5.5% (Figure 7 and 8).

A pre-planned pooled data analysis combining the data of the two comparative trials eventually established superiority of UPA over LNG. Compared to LNG UPA was able to reduce the risk of pregnancy to almost one half if given up to 120 hours after UPSI. A reduction of the pregnancy rate by almost two thirds compared to LNG was observed when given within 24 hours after UPSI implying the recommendation that UPA should be taken as soon as possible after an UPSI [14].

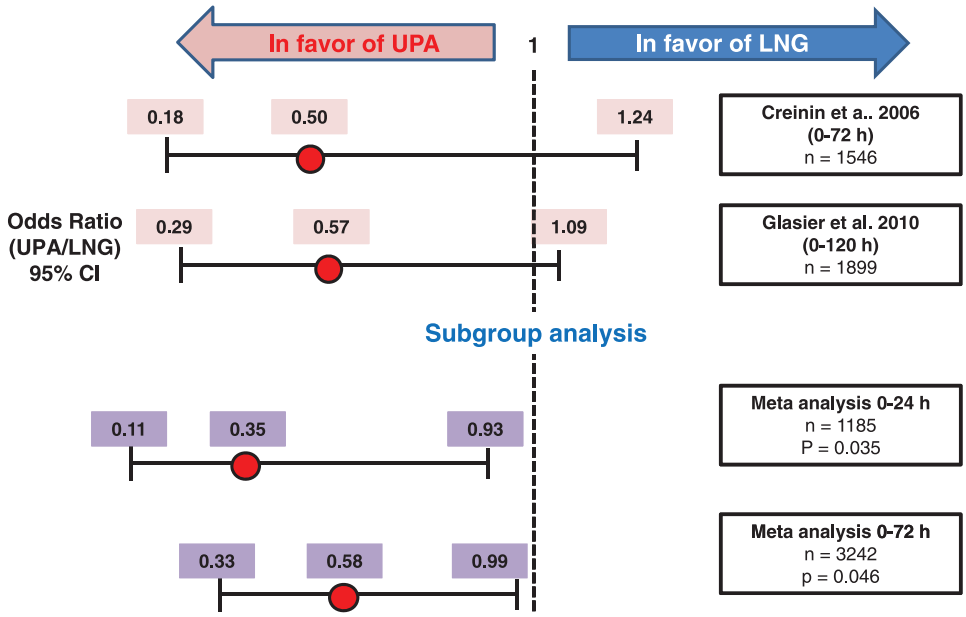
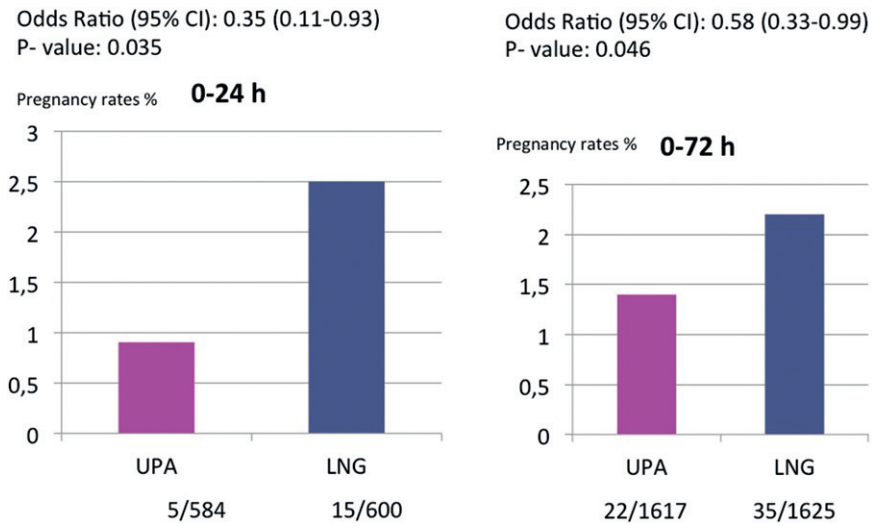


Figure 7. Pooled analysis of contraceptive efficacy of ulipristal acetate (UPA) versus levonorgestrel (LNG) (According to data of [37,14]).

Figure 8. Comparison of pregnancy rates (0–24 h; left and 0–72 h; right) in the pooled data anaylsis of Glasier et al. [14].



Factors influencing EC efficacy

In the meta-analysis by Glasier et al. [14] on LNG versus UPA factors associated with EC failure were analyzed. Body mass index (BMI) had the most significant impact on risk for pregnancy where this risk was more than 3 times greater for women with BMI 30 and above, compared with women with BMI under 25 with any of the EC methods. The effect of BMI on pregnancy rate was more pronounced in women treated with LNG than UPA. The efficacy of LNG decreased rapidly with increasing BMI and the analysis showed no difference from pregnancy rates expected among women not using EC at a BMI of 26 if treated with LNG compared to BMI 35 if treated with UPA. When weight instead of BMI was a covariate in analyses the limit of efficacy was reached at 70 kg for LNG compared with 88 kg in women having taken UPA. Other significant factors found to influence pregnancy risk were the cycle-day of UPSI, with the highest risk on the day before ovulation, and also if further acts of UPSI occurred after the intake of EC (Table 5). No significant differences between the treatment groups (LNG versus UPA) were observed on these effects on pregnancy risk [14] (Table 6). The observed high risk of Ec failure

Table 5. Risk factors for failure of EC ("metaanalysis RCT's UPA versus LNG)($n = 3445$)*) no treatment group effect (according to Glasier et al. 2010) [14] (*UPSI = unprotected intercourse).

	Odds Ratio (95% CI)
Cycle day of intercourse	4.4 (2.3–8.2) $p < 0.0001$
Further UPSI*	4.6 (2.2–9.0) $p < 0.0002$
BMI Obese vs. normal	3.6 (1.96–6.53) $p < 0.0001$
Overweight vs. normal	1.53 (0.75–2.95)

Table 6. Risk of pregnancy compared to normal BMI.

BMI group	LNG OR (95% CI)	UPA OR (95% CI)
Overweight vs. normal	2.09 (0.86–4.87)	0.97 (0.27–2.83)
Obese vs. normal	4.41 (2.05–9.44)*	2.62 (0.89–7.00)

*$p = 0.0002$; limit of efficacy: LNG 26 kg/m^2 (weight 70 kg); UPA 35 kg/m^2 (weight 88 kg) (According to [14]).

at intercourse at the time of ovulation is consitent with the mechanism of action with no action of EC after ovulation has occurred.

Copper IUD

Copper is toxic to the ovum and sperm and thus the copper-bearing intrauterine device is effective immediately after insertion and works primarily by inhibiting fertilisation [45a,45b,46].

A systematic review on mechanisms of action of IUDs showed that both pre- and postfertilisation effects contribute to efficacy. If fertilisation has already occurred, it is accepted that there is an anti-implantation effect [47,48].

The use of copper IUD for EC is an ''off-label'' use; nevertheless in the UK this option is taken by 15% of EC-users [49], especially due to the high contraceptive efficacy (>99%) and when long term contraception is preferred.

There are several clinical trials analyzing the contraceptive potential of copper IUD for EC [50–54]. To avoid uterine infections vaginal and cervical infections must be excluded and according to parity, the phase of the menstrual cycle a cervical dilatation might be necessary. Furthermore the type of copper IUD must be selected.

The smallest one is actually the frameless copper IUD, GyneFix® (Contrel, Belgium: www.wildemeersch.com), according to a personal information by the inventor D. Wildemeersch [55]. It can be used for EC [56]. Unfortunately the small GF200 should have been used but didn't exist at that time. The small GF200 is the standard for all normal uteri (<8.5 cm sound length); its registered for EC use in the European Union. Other IUDs with registration for EC are Multiload-Cu 250 (CE), Multiload-Cu 375 (CE) and Multiload-Cu 375 SL (CE). Use of IUDs without this registered indication for use as EC is ''off-label''.

The main disadvantage of IUD that is an invasive procedure, and it is required trained providers and sterilized facilities.

Cochrane Analysis

In a Cochrane analysis Cheng et al. [13] analysed trials of postcoital contraception, looking at 100 trials enrolling a total number of 55 666 women. Most of these trials, i.e. 86 out of 100, were done in China.

Mifepristone: Meta-analysis indicated that mid-dose mifepristone (25–50 mg) (20 trials; RR 0.64; 95% CI 0.45 to 0.92) or low-dose mifepristone (<25 mg) (11 trials; RR 0.70; 95% CI 0.50 to 0.97) were significantly more effective than LNG, but the significance was marginal when only high-quality studies were included (4 trials; RR 0.70; 95% CI 0.49 to 1.01). Low-dose mifepristone was less effective than mid-dose mifepristone (25 trials; RR 0.73; 95% CI 0.55 to 0.97). This difference was not statistically significant when only high-quality trials were considered (6 trials; RR 0.75; 95% CI 0.50 to 1.10). Mifepristone (all doses) (3 trials; RR 0.14; 95% CI 0.05 to 0.41) were more effective than the Yuzpe regimen in preventing pregnancy.

Levonorgestrel: Single-dose LNG (1.5 mg) showed similar effectiveness as the standard two-dose regimen (0.75 mg 12 h apart) (3 trials; RR 0.84; 95% CI 0.53 to 1.33). This conclusion was not modified by the time elapsed from intercourse to treatment administration. LNG (5 trials; RR 0.54; 95% CI 0.36 to 0.80) were more effective than the Yuzpe regimen in preventing pregnancy.

Ulipristal acetate appeared more effective (2 trials; RR 0.63) than LNG at a marginal level ($p = 0.09$) within 72 hours of intercourse. Regarding effectiveness in relation to the time of administration, women who took LNG within 72 hours of intercourse were significantly less likely to be pregnant than those who took it after 72 hours (4 trials; RR 0.51; 95% CI 0.31 to 0.84). It was not evident that the coitus-treatment time affected the effectiveness of mifepristone and UPA. Single-dose LNG (1.5 mg) showed similar effectiveness as the standard two-dose regimen (0.75 mg 12 h apart) (3 trials; RR 0.84; 95% CI 0.53 to 1.33). This conclusion was not modified by the time elapsed from intercourse to treatment administration. Mifepristone (all doses) (3 trials; RR 0.14; 95% CI 0.05 to 0.41) and LNG (5 trials; RR 0.54; 95% CI 0.36 to 0.80) were more effective than the Yuzpe regimen in preventing pregnancy.

Gestrinone: One trial compared gestrinone with mifepristone. No significant difference of effectiveness was identified in this trial (996 women; RR 0.75; 95% CI 0.32 to 1.76).

All methods of EC were safe. Nausea and vomiting occurred with oestrogen-containing EC methods and progestogen and anti-progestogen methods caused changes in subsequent menses. LNG users were more likely to have a menstrual return before the expected date, but UPA users were more likely to have a menstrual return after the expected date. Menstrual delay was the main adverse effect of mifepristone and seemed to be dose-related.

Conclusion: Intermediate-dose mifepri-stone (25–50 mg) was superior to LNG and Yuzpe regimens. Mifepristone low dose (<25 mg) may be more effective than LNG (0.75 mg two doses), but this was not conclusive. UPA may be more effective than LNG. LNG proved to be more effective than the Yuzpe regimen. The copper IUD was the most effective EC method and was the only EC method to provide ongoing contraception if left in situ.

Summary

1. Mifepristone

Cochrane conclusions [13]:

– Intermediate-dose mifepristone (25–50 mg) was superior to LNG and Yuzpe regimens. Mifepristone low dose (<25 mg) may be more effective than LNG (0.75 mg two doses), but this was not conclusive.

– It was not evident that the coitus-treatment time affected the effectiveness of mifepristone.

Contraceptive failure: about 1.5% for 10 and 25 mg mifepristone up to 5 days after UPSI.

2. Levonorgestrel

LNG 1.5 mg (single dose) is effective as postcoital contraceptives up to 5 days **[57].**

Cochrane conclusions [13]:

– LNG proved to be more effective than the Yuzpe regimen.

– Regarding effectiveness in relation to the time of administration, women who took LNG within 72 hours of intercourse were significantly less likely to be pregnant than those who took it after 72 hours (4 trials; RR 0.51; 95% CI 0.31 to 0.84).

Contraceptive failure: about 3%.

3. Levonorgestrel (1.5 mg)(single dose) and ulipristal acetate

Clinical trials analysing contraceptive efficay

UPA versus LNG

UPA and LNG are effective as postcoital contraceptives up to 5 days.

Cochrane conclusions [13]:

– **UPA** appeared more effective (2 trials; RR 0.63) than **LNG** at a marginal level ($p = 0.09$) within 72 hours of intercourse.

4. Ulipristal acetate

There are no clinical data demonstrating that the contraceptive efficacy of UPA declines by time elapsed after UPSI up to 5 days after UPSI.

Cochrane conclusions [13]: It was not evident that the coitus-treatment time affected the effectiveness of UPA.

Looking a specific subsets of data is situation is a little bit different:

– Viceversa Fine et al. [38]. and Glasier et al. [14]. showed lower pregnancy rate after 72 hours than in the time window before. The low (zero) pregnancy rate in [14]. studies may depend on bias (knowledge that early use is better than late use) and small number of subjects are these data should not be overestimated.

– Comparing the time frame from 25–48 hours to less than 24 hours both Creinin et al. [37] and Glasier et al. [14]. showed a lower pregnancy rate for the early use of UPA - but no statistical significance is given for this observation.

Contraceptive failure: about 1.5%.

Use of UPA as early as possible - is there a clinical need?

Depending on the long existing knowledge from earlier EC studies such as [18] indicating that emergency contraceptives should be used as early as possible, there is an upcoming discussion to use UPA as early as possible to prevent preovulatory follicular growth and suppress ovulation - even this hypothesis is not supported by any clinical trial and also Cheng et al. [13] did not see that coitus-treatment time affected the effectiveness of UPA. However in the metaanalysis by Glasier et al it is clear that if used within 24 hours form the UPSI UPA was three times as effective as LNG and thereafter twice as effective. For practical and efficacy reasons it is therefore important to advise women to use ECP as soon as possible (see also [13]).

Ideally they should be provided with pills in advance or EC pills should be available OTC. It is also important to remember that - if possible - the Cu-IUD is the most effective EC method probably because it acts both to prevent fertilization but also to prevent implantation, but worldwide insertion of a copper IUD is ''off label'', not for the small copper chain-IUD GynFix® (Contrel/Belgium) in the European Union. At present all European countries except Germany and Swizerland have LNG available OTC. Hopefully UPA will also be available in short.

If the woman vomits within three hours of taking the medicine she should take another tablet. UPA (ellaOne®) can be taken at any time during the menstrual cycle. Possible drug interactions must be considered (see SmPC).

Resume or initiate contraception?

The question when can a women resume or initiate contraception after taking emergency contraceptive pills is addressed in a systematic review by Salcedo et al. [58]. The drug manufacturer advises continuation or initiation of routine contraception as soon as possible after use of UPA, with concomitant use of a reliable barrier method until next menses. However, a theoretical concern exists that given UPA's function as a selective progesterone receptor modulator, coadministration of a progestin could decrease its effectiveness as an emergency contraceptive. Initiation of hormonal contraception following LNG or the Yuzpe regimen for EC carries no similar concern for decreased method effectiveness.

5. Copper-IUD

Cochrane conclusions [13]: The copper IUD was the most effective EC method and was the only EC method to provide ongoing contraception if left in situ.

Contraceptive failure: less than 0.1%.

IUD insertion might not be acceptable for every patient. Furthermore IUD-insertion is an invasive procedure and it is required trained providers and sterilized facilities.

The insertion of an copper IUD is an ''off-label'' procedure; only the small copper chain GyneFix IUD (can be also used for nullipara) is registered in the European Community for EC. Other IUDs with registration for EC are Multiload-Cu 250 (CE), Multiload-Cu 375 (CE) and Multiload 375 SL (CE). Use of IUDs without this registered indication for use as EC is ''off-label''.

6. Clinical conclusions

EC is the only method that women can use after having sexual intercourse without contraceptive protection to avoid becoming pregnant. It could be a powerful instrument to prevent unwanted pregnancies if widely available and acceptable. However it should be pointed out that EC is not as effective as regular birth control methods.

Mifepristone offers a high contraceptive efficay when used for EC in a dosage of 25 mg as a single dosage. There is a low side effect profile. The product is mainly available in china - in most other countries the product is not on the market due to potential abortifacient action.

The market launch of UPA (ellaOne®) in September 2009 allows for an effective, and safe method of postcoital contraception. UPA is a first-in-class progesterone receptor modulator specifically developed for EC. It has been demonstrated to be highly efficacious versus LNG for intake within 24 hours as well as for intake up to 72 hours after UPSI. Furthermore, UPA maintains its efficacy up to 5 days after UPSI, matching the survival time of sperms. UPA 30 mg is as well-tolerated as LNG. Therefore UPA represents a veritable breakthrough in EC technology with a clear-cut medical advantage over LNG. Although the main mechanism of action of both LNG and UPA is preventing follicular rupture and ovulation the 'window of effect' for LNG seems to be rather narrow, beginning after selection of the dominant follicle, and ending when LH begins to rise. In contrast, UPA has been demonstrated to have a direct inhibitory effect on follicular rupture. This allows UPA to be effective even when administered shortly before ovulation when the LH surge has already started to rise, a time period when use of LNG is no longer effective. The differences in mechanisms of action explain the higher efficacy demonstrated for UPA to prevent pregnancy for both early and late use of EC.

Nevertheless patients must be informed about the risk becoming pregnant using the different hormonal methods and that the ''off label'' use of an copper IUD would provide the highest (>99%) contraceptive efficacy.

Declaration of interest

Kristina Gemzell-Danielsson has served on medical advisory boards for HRA Pharma and Bayer AG. Thomas Rabe declares that he received a honorarium and reimbursements of travel expenses from Bayer AG, HRA Pharma, MSD and Teva for national and international lectures, advisory boards and consultancy. Linan Cheng has served on medical advisory boards for HRA Pharma, Bayer AG, Zi Zhu Pharmaceutical Ltd and Regenex Corporation Co. Ltd.

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