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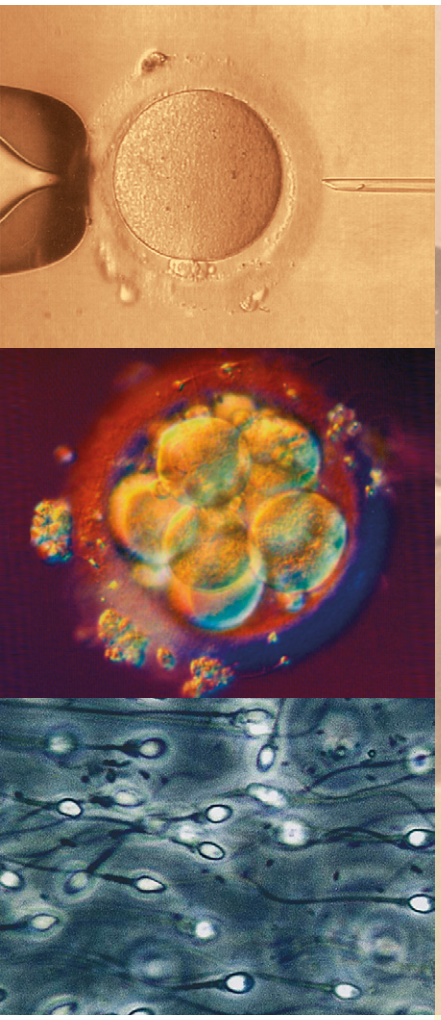

**Emergency Contraception**

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# Emergency Contraception

K. Gemzell-Danielsson[1], T. Rabe[2]

There have been numerous attempts to control fertility after unprotected sexual intercourse. 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, known as the Yuzpe regimen. The first dose had to be taken within 72 hours of unprotected intercourse, a second one 12 hours later. Later on, levonorgestrel 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 levonorgestrel pill that combined good efficacy with a high ease of use. It has become the standard method used up to this day in most countries. Since the mid 1970s copper IUDs have been used for emergency contraception, which show a high efficacy. Their disadvantages lie in the fact that emergency contraception is considered an off label use and that they might not be acceptable for every patient. Mifepristone in doses of 10 or 25 mg is being used successfully as an emergency contraceptive in China, but has never received any significant consideration in Western countries. The most recent development is the approval of the selective progesterone receptor modulator ulipristal acetate in the dosage of 30 mg for emergency contraception up to 5 days after unprotected intercourse, combining the safe and easy application of the single dose levonorgestrel pill with an even higher efficacy.

Several efficacious and easy to use methods for emergency contraception are available on the market today with the most widely spread being levonorgestrel 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 after unprotected intercourse. Its limitations are the non-optimal efficacy which is decreasing the later the drug is taken and the fact that it can only be used for up to 72 hours after UPSI. 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 unprotected intercourse. Recently the selective progesterone receptor modulator (SPRM) ulipristal acetate in the dose of 30 mg has been introduced in Europe for emergency contraception. It has shown to be more efficacious than levonorgestrel and can be used for up to 120 hours after unprotected intercourse.

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. **J Reproduktionsmed Endokrinol 2010; 7 (Special Issue 1): 73–7.**

**Key words:** emergency contraception, ulipristal acetate, levonorgestrel, "morning after pill", postcoital contraception

## Introduction

There has been an interest in using synthetic steroids for postcoital contraception for several decades now; a first publication on 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]. 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 early 1970s. Albert Yuzpe developed the Yuzpe regimen named after him [4], and in 1975 a method was introduced that used gestagen only [5]; the same year saw the launch of a copper spiral 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 gestagen 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 and the Yuzpe regimen and after that began to promote the use of the levonorgestrel method [6, 7]. More recently progesterone receptor modulators have been developed for emergency contraception [8].

## 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 ethinyl estradiol and 0.5 mg levonorgestrel; in this case the first dose is taken within 72 hours after having unprotected sexual intercourse, 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 levonorgestrel.

In case of unprotected sexual intercourse 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 meta-analysis 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,

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**Table 1:** 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 hours | Used to be approved for the Netherlands; otherwise, only little use | 75 % | Randomised trial enrolling 250 women | Obsolete!! High risk of VTE! |
| **Mifepristone** (10 or 25 mg with 25 mg being more effective [Cochrane review by Cheng et al.] | 0–120 hours | Used in China for postcoital contraception; off-label available in several countries | > 85 % | 3 randomised trials with > 2,300 women | Not available for postcoital contraception in Europe |
| **Estrogen/gestagen** (100 µg ethinyl estradiol and 0.5 mg levonorgestrel as 2 doses 12 hours apart) | 0–72 hours | Since 1980 approved in some countries (e. g. Britain, Holland); unlicensed available as a combination of several oral combination pills | 75 % | Meta-analysis of 10 trials and > 5,000 women | Available, but off-label |
| **Levonorgestrel** (0.75 mg in 2 doses taken 12 hours apart) | 0–72 hours | Approved in East Europe and Asia | 75–85 % | 2 randomised trials enrolling > 2,500 women | |
| **Levonorgestrel** (1.5 mg as a single dose) | 0–72 hours | Available worldwide; approved in Germany | 75–85 % Decreasing over time; it has been shown that this regimen and the one above are equally effective | | Standard method for postcoital contraception |
| **Ulipristal** (30 mg as a single dose) | 0–120 hours | European approval in May 2009; launched on the German market in September 2009 | > 85 % Superior to Levonorgestrel; constant over time | 2 randomised trials with > 2,000 women | Launch in European market in 10/2009 |
| **Copper IUD** | 0–120 hours after the earliest calculated day of ovulation | Available worldwide, but not approved for postcoital contraception | 99 % | Meta-analysis of 20 trials and > 8.000 women | Available, but off-label |

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-gestagen 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 (Tab. 1).

## Levonorgestrel Method

This method comprises the intake of 0.75 mg levonorgestrel within 72 hours after unprotected intercourse and twelve hours later. In a large-scale, double-blinded trial done by the WHO [12], enrolling 1,998 women in 14 countries, the levonorgestrel method was compared to the Yuzpe regimen. Among those women using levonorgestrel the expected pregnancy rate decreased by 85 % (95 %-CI: 74–93 %). Only 23 % of all women in the levonorgestrel 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 levonorgestrel 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 unprotected intercourse 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 unprotected intercourse. 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 levonorgestrel 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].

## Mifepristone

Mifepristone is an anti-gestagen which was mainly developed to allow medical termination of pregnancies. 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 unprotected sexual intercourse 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 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 emergency contraception 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].

## Cochrane Analysis

In a Cochrane analysis Cheng et al. [13] analysed trials of postcoital contraception, looking at 81 trials enrolling a total number of 45,482 women. Most of these trials, i. e. 70 out of 81, were done in China. Using the levonorgestrel method, there were more pregnancies than taking a medium dose of mifepristone (25–50 mg) (15 trials; RR 2.01; CI: 1.27–3.17) or a lower dose of mifepristone (< 25 mg) (9 trials; RR 1.43; CI: 1.02–2.01). Still, a lower dose of mifepristone was less effective than its medium dose (20 trials; RR 0.7; CI: 0.49–0.92), but this difference ceased to be significant when analysing the high-quality trials only (RR: 0.5; CI: 0.–1.0). Levonorgestrel as a single dose (1.5 mg) was as effective as the double dose of 0.75 mg levonorgestrel taken twelve hours apart (2 trials, 3,830 women; RR 0.77; CI: 0.45–1.30). Levonorgestrel was more effective than the Yuzpe regimen (2 trials; RR: 0.51; CI: 0.31–0.83). CDB-2914 (ulipristal), a second-generation progesterone receptor modulator, is probably as effective as levonorgestrel (1 trial, 1,549 women, RR: 1.89; CI: 0.75–4.64). Currently available are the following methods: the single use of a combination of estrogen and gestagen (ethinyl estradiol together with levonorgestrel); the single use of gestagen (levonorgestrel); the use of the mifepristone (Mifegyn, Mifeprex), and the insertion of a copper IUD (see Tab. 1).

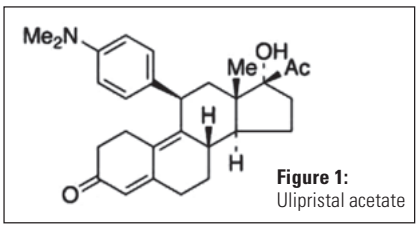

**Figure 1:** Ulipristal acetate

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 – this method will be discussed in detail in the following chapter.

## Ulipristal – A Progesterone Receptor Modulator

### Substance

Ulipristal acetate is the first selective progesterone receptor modulator (SPRM) approved for emergency contraception (Fig. 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

Ulipristal acetate 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 ulipristal acetate was granted marketing authorisation for Europe by the EMEA. The indication is the one for emergency contraception up to 120 hours (5 days) after unprotected sexual intercourse or contraceptive failure.

### Mechanism

Ulipristal acetate (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 ulipristal acetate, 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). 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.

### Studies of Receptor Binding

In vitro, ulipristal acetate competitively binds to the progesterone receptor, the glucocorticoid receptor and the andro-

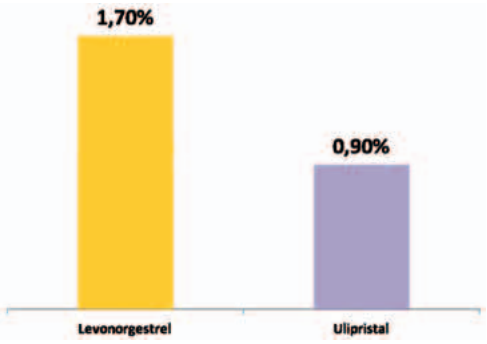


**Figure 2:** Comparison of pregnancy rates (0–72 h). Better contraceptive effectiveness of 30 mg ulipristal compared to 1.5 mg Levonorgestrel given as a single dose within 3 days after unprotected intercourse. Mod. from [37].

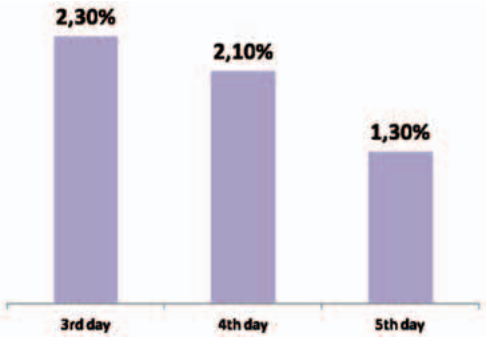


**Figure 3:** Decrease of pregnancy rate after intake of 30 mg of ulipristal up to 5 days after unprotected intercourse. Mod. from [38].

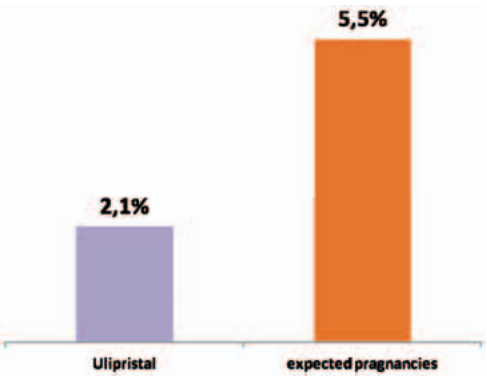


**Figure 4:** Pregnancy rate after intake of 30 mg of ulipristal 3 to 5 days after unprotected intercourse compared to expected pregnancies (calculated according to Trussel et al., 14). Mod. from [38].

gen receptor. Simultaneously, it shows only a low affinity to estrogen receptor or mineralocorticoid receptor. In addition to that, ulipristal acetate 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. Ulipristal acetate 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).

## Genotoxicity

No genotoxic potential.

## 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.

## Summary of Clinical Data

Two clinical trials (Phase II: 50 mg unmicronized ulipristal acetate versus 1.5 mg levonorgestrel as a single dose; Phase III: 30 mg micronized ulipristal only) saw the examination of women who used emergency contraception between 0 and 72 hours or 48 and 120 hours after unprotected intercourse or contraceptive failure. The results of both trials showed that ulipristal acetate (UPA) was at least as suitable for the purpose of emergency contraception as levonorgestrel (LNG). The first trial (0–72 hours) shows a significantly higher efficacy of 30 mg ulipristal acetate compared to 1.5 mg levonorgestrel as a single dose, with pregnancy rates of 0.90 % for ulipristal acetate versus 1.70 % for levonorgestrel (Fig. 2). The contraceptive efficacy of ulipristal acetate maintained over five days (Fig. 3). The second trial revealed pregnancy rates of 2.1 % for ulipristal acetate versus the expected pregnancies of 5.5 % (Fig. 4).

An additional phase III trial examined the efficacy of 30 mg micronized ulipristal acetate versus 1.5 mg levonorgestrel for up to 120 hours after unprotected sexual intercourse. This trial proved non-inferiority of ulipristal acetate, again with a trend towards higher efficacy for ulipristal acetate. A meta-analysis combining these data with the aforementioned phase II trial eventually established superiority of ulipristal acetate over levonorgestrel. Compared to levonorgestrel ulipristal acetate was able to reduce the risk of pregnancy to almost one half if given up to 120 hours after unprotected intercourse. A reduction of the pregnancy rate by almost two thirds compared to levonorgestrel was observed when given within 24 hours after unprotected intercourse implying the recommendation that ulipristal acetate should be taken as soon as possible after an unprotected intercourse [14].

## Side Effects

The frequency of side effects after taking 30 mg ulipristal acetate is comparable to that of taking 1.5 mg levonorgestrel. Both forms of treatment only featured very rare cases of vomiting (Fig. 5). For ulipristal acetate a higher rate of nausea was observed, however, the overall rate of less than 30 % was very low.

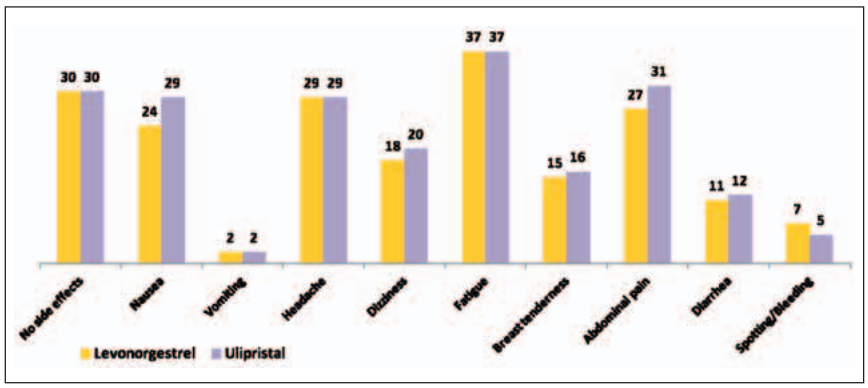


**Figure 5:** Side effects of ulipristal acetate 30 mg compared to Levonorgestrel 1.5 mg as a single dose. Mod. from [37].

## Conclusion

Emergency contraception 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 emergency contraception is not as effective as regular birth control methods. The market launch of ulipristal (ellaOne) in September 2009 allows for an effective, and safe method of postcoital contraception.

Ulipristal acetate 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 unprotected intercourse. Furthermore, UPA maintains its efficacy up to 5 days after unprotected intercourse, matching the survival time of sperms. UPA 30 mg is as well-tolerated as LNG. Therefore UPA represents a veritable breakthrough in emergency contraceptive 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.

### References:


1. Demers L. The morning-after pill. N Engl J Med 1971; 284: 1034–6.

2. FDA considers DES safe as 'morning-after pill'. JAMA 1973; 224: 1581–8.

3. Johnson JH. Contraception – the morning after. Fam Plann Perspect 1984; 16: 266.

4. Yuzpe A, Thurlow H, Ramzy I, et al. Postcoital contraception – A pilot study. J Reprod Med 1974; 13: 53–8.

5. Valle G. The problem of postcoital contraception using oral progestins. Aggiorn Ostet Ginecol 1975; 8: 127–8.

6. Task Force on Postovulatory Methods of Fertility Regulation. Randomised controlled trial of levonorgestrel versus the Yuzpe regimen of combined oral contraception for emergency contraception. Lancet 1998; 352: 428–33.

7. Guillebaud J. Time for emergency contraception with levonorgestrel alone. Lancet 1998; 352: 416–7.

8. Gemzell-Danielsson K, Meng CX. Emergency contraception: potential role of ulipristal acetate. Int J Women's Health 2010; 2: 53–61.

9. Yuzpe AA, Lancee WJ Ethinylestradiol and dl-norgestrel as a postcoital contraceptive. Fertil Steril 1977; 28: 932–6.

10. Trussell J, Rodriguez G, Ellertson C. Updated estimates of the effectiveness of the Yuzpe regimen of emergency contraception. Contraception 1999; 59: 147–51.

11. Vasilakis C, Jick SS, Jick H. The risk of venous thromboembolism in users of postcoital contraceptive pills. Contraception 1999; 59: 79–83.

12. Glasier A. Emergency postcoital contraception. N Engl J Med 1997; 337: 1058–64.

13. Cheng L, Gülmezoglu AM, Piaggio GGP, et al. Interventions for emergency contraception. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD001324. DOI: 10.1002/14651858.CD001324.pub3.

14. Glasier AF, Cameron ST, Fine PM, Logan SJ, Casale W, Van Horn J, Sogor L, Blithe DL, Scherrer B, Mathe H, Jaspart A, Ulmann A, Gainer E. Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised non-inferiority trial and meta-analysis. Lancet 2010; 13: 555–62.

15. Strayer SM, Couchenour RL. Combined oral contraceptives versus levonorgestrel for emergency contraception. J Fam Pract 1998; 47: 417.

16. von Hertzen HG, Piaggio G, Van Look PF. Emergency contraception with levonorgestrel or the Yuzpe regimen. Task Force on Postovulatory Methods. Lancet 1998; 352: 1939.

17. von Hertzen H, Piaggio G, Ding J, Chen J, Song S, Bártfai G, Ng E, Gemzell-Danielsson K, Oyunbileg A, Wu S, Cheng W, Lüdicke F, Pretnar-Darovec A, Kirkman R, Mittal S, Khomassuridze A, Apter D, Peregoudov A; WHO Research Group on Post-ovulatory Methods of Fertility Regulation. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomised trial. Lancet 2002; 360: 1803–10.

18. Piaggio G, von Hertzen H, Grimes DA, Van Look PF. Timing of emergency contraception with levonorgestrel or the Yuzpe regimen. Task Force on Postovulatory Methods of Fertility Regulation. Lancet 1999; 353: 721.

19. Ho PC, Kwan MS. A prospective randomized comparison of levonorgestrel with the Yuzpe regimen in post-coital contraception. Hum Reprod 1993; 8: 389–92.

20. Durand M, del Carmen Cravioto M, Raymond EG, Durán-Sánchez O, De la Luz Cruz-Hinojosa M, Castell-Rodríguez A, Schiavon R, Larrea F. On the mechanisms of action of short-term levonorgestrel administration in emergency contraception. Contraception 2001; 64: 227–34.

21. Marions L, Cekan SZ, Bygdeman M, Gemzell-Danielsson K. Effect of emergency contraception with levonorgestrel or mifepristone on ovarian function. Contraception 2004; 69: 373–7.

22. Marions L, Hultenby K, Lindell I, Sun X, Ståbi B, Gemzell Danielsson K. Emergency contraception with mifepristone and levonorgestrel: mechanism of action. Obstet Gynecol 2002; 100: 65–71.

23. Croxatto HB, Brache V, Pavez M, Cochon L, Forcelledo ML, Alvarez F, Massai R, Faundes A, Salvatierra AM. Pituitary-ovarian function following the standard levonorgestrel emergency contraceptive dose or a single 0.75-mg dose given on the days preceding ovulation. Contraception 2004;70: 442–50.

24. Lalitkumar PG, Lalitkumar S, Meng CX, Stavreus-Evers A, Hambiliki F, Bentin-Ley U, Gemzell-Danielsson K. Mifepristone, but not levonorgestrel, inhibits human blastocyst attachment to an in vitro endometrial three-dimensional cell culture model. Hum Reprod 2007; 22: 3031–7.

25. Müller AL, Llados CM, Croxatto HB. Postcoital treatment with levonorgestrel does not disrupt postfertilization events in the rat. Contraception 2003; 67: 415–9.

26. Ortiz ME, Ortiz RE, Fuentes MA, Parraguez VH, Croxatto HB. Post-coital administration of levonorgestrel does not interfere with post-fertilization events in the new-world monkey Cebus apella. Hum Reprod 2004; 19: 1352–6.

27. Novikova N, Weisberg E, Stanczyk FZ, Croxatto HB, Fraser IS. Effectiveness of levonorgestrel emergency contraception given before or after ovulation – a pilot study. Contraception 2007; 75: 112–8.

28. Ho PC, et al. Mifepristone: contraceptive and non-contraceptive Uses. Current Opinions Obstet Gynecol 2002; 14: 325–30.

29. Wertheimer RA. Emergency postcoital contraception. Am Fam Physician 2000; 62: 2287–92.

30. Shoupe D, Mishell DR Jr, Page MA, Madkour H, Spitz IM, Lobo RA. Effects of the antiprogesterone RU 486 in normal women. II. Administration in the late follicular phase. Am J Obstet Gynecol 1987; 157: 1421–6.

31. Ledger WL, Sweeting VM, Hillier H, Baird DT. Inhibition of ovulation by low-dose mifepristone (RU 486). Hum Reprod 1992; 7: 945–50.

32. van der Stege JG, Pahl-van Beest EH, Beerthuizen RJ, van Lunsen RH, Scholten PC, Bogchelman DH. Effects of a preovulatory single low dose of mifepristone on ovarian function. Eur J Contracept Reprod Health Care 2006; 11: 104–8.

33. Gemzell-Danielsson K, Svalander P, Swahn ML, Johannisson E, Bygdeman M. Effects of a single post-ovulatory dose of RU486 on endometrial maturation in the implantation phase. Hum Reprod 1994; 9: 2398–404.

34. Gemzell-Danielsson K, Swahn ML, Svalander P, Bygdeman M. Early luteal phase treatment with mifepristone (RU 486) for fertility regulation. Hum Reprod 1993; 8: 870–3.

35. Swahn ML, Gemzell K, Bygdeman M. Contraception with mifepristone. Lancet 1991; 12: 942–3.

36. Stratton P, Levens ED, Hartog B, Piquion J, Wei Q, Merino M, Nieman LK. Endometrial effects of a single early luteal dose of the selective progesterone receptor modulator CDB-2914. Fertil Steril 2010; 93: 2035–41.

37. Creinin MD, Schlaff W, Archer DF, et. al. Progesterone receptor modulator for emergency contraception: a randomized controlled trial. Obstet Gynecol 2006; 108: 1089–97

38. Fine P, Mathé H, Ginde S, Cullins V, Morfesis J, Gainer E. Ulipristal acetate taken 48–120 hours after intercourse for emergency contraception. Obstet Gynecol 2010; 115: 257–63.

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