

# Mechanisms of action of mifepristone and levonorgestrel when used for emergency contraception

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**An emergency contraceptive method is used after coitus but before pregnancy occurs. The use of emergency contraception is largely under-utilized worldwide. One of the main barriers to widespread use is concern about the mechanism of action. Recently, treatment with either 10 mg mifepristone or 1.5 mg of levonorgestrel has emerged as the most effective hormonal method for emergency contraception with very low side-effects. However, the knowledge of the mechanism of action of mifepristone and levonorgestrel in humans, when used for contraceptive purposes and especially for emergency contraception, remains incomplete. The objective of this review is to summarize available data on the effects of mifepristone and levonorgestrel on female reproductive functions relevant to the emergency use of the compounds. When summarized, available data from studies in humans indicate that the contraceptive effects of both levonorgestrel and mifepristone, when used in single low doses for emergency contraception, involve either blockade or delay of ovulation, due to either prevention or delay of the LH surge, rather than to inhibition of implantation.**

*Key words:* emergency contraception/endometrium/levonorgestrel/mifepristone/ovulation

## Introduction

Emergency contraception (EC) is defined as the use of any drug or device used after an unprotected intercourse to prevent an unwanted pregnancy. The use of emergency contraception is largely under-utilized worldwide. Emergency contraception has been called 'one of the best kept secrets in family planning'. One of the main barriers to widespread use is the concern about the mechanisms of action, such as impairment of implantation, or dislodgement of an implanted fetus. Emergency contraception is frequently confused with induced abortion. In many developing countries, the lack of knowledge about and access to emergency contraception may result in women resorting to unsafe abortions, which contribute significantly to maternal mortality and morbidity. It has been estimated that millions of unwanted pregnancies could be avoided if emergency contraception were widely accessible (Consensus statement of emergency contraception, 1995). An understanding of the mechanism of action of contraceptive methods is essential for the development of new methods as well as for optimizing the use of those already available. This knowledge may also influence religious, cultural and individual acceptability of contraceptive methods.

Trials on emergency contraception were first described in the 1930s using high doses of stilbestrol (Morris and van Wagenen, 1966). In the late 1970s Yuzpe introduced a regimen consisting of 0.1 mg ethinylestradiol and 0.5 mg levonorgestrel,

given within 72 h of the intercourse and repeated after 12 h (Yuzpe and Lance, 1977). The Yuzpe regimen has since been the most commonly used method. Other available methods today are the administration of levonorgestrel 0.75 mg, repeated after 12 h or in a single dose of 1.5 mg, as a single dose of 10 mg mifepristone (only available in China), or insertion of a copper intrauterine device (IUD) (Lippes *et al.*, 1979).

Recently, treatment with levonorgestrel only and mifepristone has emerged as the most effective hormonal method with very low side-effects and higher efficacy than the standard Yuzpe regimen [World Health Organization (WHO), 1998, 1999]. Following these studies, levonorgestrel 1.5 mg has become the recommended regimen. The hormonal methods are usually also considered as more convenient than the insertion of a copper IUD which is otherwise the most effective method. When 600 mg of mifepristone was administered within 72 h of an unprotected intercourse, no pregnancy occurred among 597 women treated (Glasier *et al.*, 1992; Webb *et al.*, 1992). The efficacy was shown to be higher than with the Yuzpe regimen and the incidence of side-effects such as nausea and vomiting was significantly decreased. However, a delay in the return of the menstrual bleeding was more commonly observed after mifepristone. In the study by Webb *et al.* (1992), three women who conceived after treatment but before follow-up were excluded. When the dose of mifepristone was reduced to 50 or 10 mg,

the efficacy was shown to be the same as with the higher dose, but the delay of the next menses was clearly shortened in a dose-dependent manner. Also, the interval from coitus to treatment could be extended to 120h and, in contrast to the Yuzpe regimen and levonorgestrel, there seemed to be no decrease in efficacy with time (WHO, 1999). However, in a more recent study comparing 25 and 10mg of mifepristone given within 120h of an unprotected intercourse, both doses were equally effective in preventing pregnancy but efficacy decreased with treatment delay (Xiao *et al.*, 2002). The efficacy of 10mg of mifepristone was tested further and compared to levonorgestrel, 0.75mg twice with a 12h interval or in a single dose of 1.5mg (von Hertzen *et al.*, 2002). Pregnancy rates did not differ between mifepristone and levonorgestrel treatment in divided or single doses when taken within 5 days of unprotected intercourse (1.5%). Side-effects were mild and similar between treatment groups. Women who took levonorgestrel had earlier menses than those who took mifepristone. An advance in the next menses of >7 days occurred in 15% of women following levonorgestrel and 9.4% following mifepristone while a delay in the next menses of >7 days occurred in 5 and 9% for levonorgestrel and mifepristone respectively.

In all WHO studies, efficacy was calculated as 'intention-to-treat' which means that all pregnancies were included, even those resulting from intercourse after treatment but before follow-up.

Although both mifepristone and levonorgestrel are highly effective when used for emergency contraception, the knowledge of the mechanism underlying these effects remains incomplete. The objective of this review is to summarize available data on the effect of mifepristone and levonorgestrel on female reproductive functions relevant to emergency use of the compound.

Unprotected intercourse may occur, and emergency contraception may be used, at any time during the menstrual cycle but it is only during a limited period, from ~5 days before to 1 day after ovulation that unprotected intercourse may result in a pregnancy (Wilcox *et al.*, 1995). To be effective, postcoital treatment could theoretically target one or several of the following events: sperm transport and function, follicular development, ovulation, fertilization, embryo development and transport, endometrial receptivity and implantation and corpus luteum function (Table I). In the following we address the effects of mifepristone and levonorgestrel on each of these reproductive processes

## Effects on human sperm transport and function

### Mifepristone

Progesterone triggers the acrosome reaction of capacitated human sperm *in vitro*. A rise in intracellular calcium is one of

**Table I.** Possible targets for emergency contraception

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|  |
|--|
| Sperm transport and function             |
| Follicular development                   |
| Ovulation                                |
| Fertilization                            |
| Embryo development and transport         |
| Endometrial receptivity and implantation |
| Corpus luteum                            |

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the first events observed following the binding of progesterone to the sperm cell. There are conflicting results on the effect of mifepristone on sperm functions *in vitro*. Some authors report that the influx of calcium and the acrosome reaction can be inhibited by mifepristone (Serres *et al.*, 1994; Yang *et al.*, 1994). However, it has also been reported that mifepristone is ineffective in inhibiting the progesterone-mediated calcium increase in sperm (Blackmore *et al.*, 1991). A single dose of 200mg mifepristone when given to 12 healthy, male volunteers did not seem to affect baseline levels of sperm intracellular calcium or the capacity of sperm to increase intracellular calcium following exposure to progesterone (our unpublished data). Incubation of sperm samples with 100 µmol/l mifepristone during capacitation led to a decrease in basal intracellular calcium levels but the response to progesterone was unaffected. Results from our studies indicate that mifepristone may decrease basal intracellular calcium levels of capacitated sperm. The concentration of mifepristone required to cause such an effect is, however, several times higher than the drug level reached in seminal plasma after treatment of male volunteers *in vivo* (our unpublished data).

### Levonorgestrel

Kesserü *et al.* (1974) showed that treatment with 0.4mg of levonorgestrel within 3–10h of an unprotected intercourse had a number of effects. It decreased the number of sperm recovered from the uterine cavity beginning 3h after treatment, caused pronounced alkalization of the intrauterine fluid beginning at 5h, which immobilized the sperm, and increased the viscosity of the cervical mucus, beginning at 9h after treatment. Effects described on sperm function *in vitro* seem to be dose dependent and results are slightly divergent. Yeung *et al.* (2002) reported a dose-dependent effect on zona-binding capacity and sperm velocity but no effect on acrosome reaction after exposure of human sperm to levonorgestrel whereas a dose-dependent increase in the rate of acrosome reaction was noted in another study (Bahamondes *et al.*, 2003).

Taken together, these data indicate that levonorgestrel or mifepristone in doses relevant for emergency contraception have no direct effect on sperm function. The observations described by Kesserü *et al.* are probably of importance when levonorgestrel is used as a regular contraceptive but unlikely to be the main mechanism of action of levonorgestrel used for EC since sperm can be retrieved from the Fallopian tube within min after insemination (Kunz *et al.*, 1996).

## Follicular development

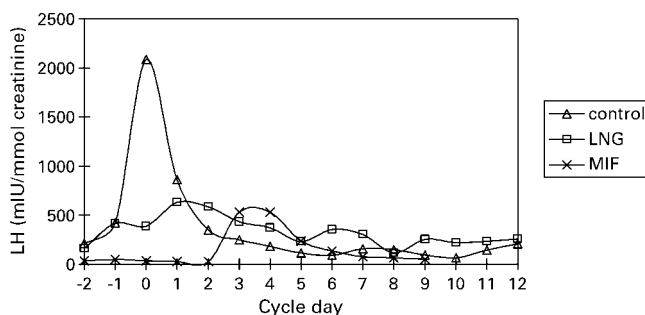
### Mifepristone

The effect of mifepristone during the menstrual cycle is well known to be dependent on the dose given and the time of treatment. Administration of mifepristone during the pre-ovulatory phase of the menstrual cycle either disrupts follicular development or inhibits ovulation. A low dose (<50mg) of mifepristone may lead to a delay in follicular maturation, which, as soon as the influence of mifepristone is over, continues to an ovulation that will be delayed. Alternatively, ovulation returns when a new leading follicle has been recruited. The follicle may also remain unruptured until the end of the cycle. When ovulation occurs,

the following luteal phase seems to be normal with normal endometrial development and function, as judged by implantation rates (Swahn *et al.*, 1988; Ghosh *et al.*, 1997). Thus, mifepristone blocks or delays ovulation in a dose-dependent fashion. At doses of 1–10 mg, ovulation is delayed but not necessarily abolished (Spitz *et al.*, 1993; Marions *et al.*, 2002). At higher doses, 200–600 mg, a new follicle is often recruited (Liu *et al.*, 1987; Shoupe *et al.*, 1987), so that a single 600 mg dose is more likely to cause a 1 week delay in menses (36%) than 10 mg (18%) (WHO, 1999).

Administration of 5 mg mifepristone when follicular diameter is 6–11 mm, i.e. before selection of the dominant follicle, has no effect on follicular development (Croxatto *et al.*, 1995). A single dose of 5 mg administered when the leading follicle had reached a diameter of 12–14 mm retarded its growth for 12–48 h after treatment (Croxatto *et al.*, 1995). Similar results were seen after daily treatment with 5 mg for 3 days at the same follicular stage. These observations indicate that mifepristone interrupts follicular growth after selection of the dominant follicle. This effect may be related to an increase in progesterone receptors (PR) in theca and granulosa cells of the dominant follicle as it approaches maturation (>12 mm) (Iwai *et al.*, 1990). Higher doses (3 mg/kg) resulted in collapse of the dominant follicle and delayed ovulation until a new follicle had been recruited (Liu *et al.*, 1987). This effect may be related to the decrease in FSH and LH, which is induced by higher doses of mifepristone (Liu *et al.*, 1987; Permezel *et al.*, 1989). At the pituitary level, mifepristone does not block the 'rise' in progesterone, it blocks the ability of progesterone to act on PR in the pituitary to facilitate the LH surge (Batista *et al.*, 1992, 1994). In women with hypothalamic amenorrhoea, mifepristone delays the mid-cycle gonadotrophin surge and ovulation, despite the exogenous administration of GnRH (Batista *et al.*, 1994).

When a single dose of 10 mg mifepristone was given to six women at a follicular diameter of >15 mm, or ~2 days prior to the LH surge, the LH surge was delayed or inhibited in all subjects (Figure 1) (Marions *et al.*, 2002). However, no changes in pregnanediol- or estrone-glucuronide levels in the luteal phase could be seen compared to controls. Unfortunately, repeated ultrasound examinations during the whole cycle were only performed in two of the six subjects. In both subjects follicles



**Figure 1.** Effect of levonorgestrel (LNG) (0.75 mg twice) or mifepristone (MIF) (10 mg single dose) on urinary LH. The concentrations are expressed as ratios to creatinine. LNG or MIF were administered in different cycles to seven women on day -2, which was defined as the day on which the follicle size corresponded to that seen 2 days before the LH peak in the control cycle.

continued to grow, exceeding the size seen in the control cycle, and the LH surge was delayed. Follicular rupture occurred at a diameter of 25 mm in one woman but remained unruptured in the other woman. When follicular growth and the luteal phase hormonal levels were further assessed, ultrasound showed various effects on follicular development (Marions *et al.*, 2004). The mean diameter of the leading follicle at treatment on day LH-2 was 18.1 mm. Among seven women, follicular development was arrested in three of them. In three women follicular development was delayed for 2–3 days and in one woman the growing follicle remained unruptured until the end of the cycle. No signs of follicle rupture were observed by ultrasound. Luteal phase urinary pregnanediol levels increased following treatment, but the increase was delayed and reduced compared to the control cycle. Cycle length was slightly prolonged. There was a difference between the effect of treatment on estradiol- and pregnanediol-glucuronide levels in these two studies (Marions *et al.*, 2002 and 2004). However, the reason for the difference is probably due to the small sample sizes.

### Levonorgestrel

Treatment with 0.75 mg levonorgestrel twice, 12 h apart, on approximately day LH-2 inhibited the LH peak in all women studied (Figure 1) (Marions *et al.*, 2002, 2004). Further assessment revealed that luteal phase pregnanediol- and estrone-glucuronide levels slightly but significantly differed from controls (Marions *et al.*, 2004). Urinary glucuronide levels were decreased compared to controls but similar to the levels observed following mifepristone. Cycle length was slightly shorter compared to control cycles. Ultrasound revealed that follicular development was either arrested ( $n = 3$ ) or that the treatment had resulted in a persistent unruptured follicle ( $n = 4$ ).

In a similar study, 12 women received 0.75 mg twice with 12 h interval pre-ovulatory (Hapangama *et al.*, 2001b). When the treatment was given on day LH-2 or-3, the LH peak was inhibited. In contrast, the treatment given on day LH-1 or on the day of the LH peak did not inhibit ovulation. Luteal phase LH levels were decreased, as well as the cycle length. The cycle was monitored by daily urinary samples used for the determination of LH. No ultrasound measurements were performed. Similar results were obtained in the rat where treatment with levonorgestrel during the luteal phase was shown to block ovulation, totally or partially (Müller *et al.*, 2003). The closer to ovulation the treatment was given the less was the effect. Furthermore, treatment with levonorgestrel in the rat and monkey does not affect fertilization or implantation (Müller *et al.*, 2003).

Mifepristone and levonorgestrel thus seem to affect follicular development after selection of the dominant follicle but before the rise in LH has begun. The effect on follicular development and ovulation varies between the delayed follicular development, and arrested or persistent unruptured follicles. The LH peak is either blocked or delayed and blunted.

### Oocyte maturation and fertilization

There are no data on the direct exposure of human embryos to mifepristone or levonorgestrel. Exposure of mifepristone to monkey embryos did not affect embryo development or their

ability to implant (Wolf *et al.*, 1989). An adverse effect of levonorgestrel seems unlikely since gestagens are commonly administered to facilitate implantation following assisted reproduction such as IVF.

To investigate if mifepristone interferes with gonadotrophin-induced oocyte maturation and fertilization, clomiphene was given for 5 days for stimulation of follicular growth to 40 volunteers (Messinis and Templeton, 1988). On day 16, 20 women received 100 mg mifepristone 1 h before induction of ovulation with injection of 5000 IU of hCG. Laparoscopy (for tubal sterilization) was performed 34 h after hCG and all follicles with a diameter of >15 mm were aspirated, and collected oocytes submitted to IVF. The 20 women not receiving mifepristone served as a control group. The number of retrieved oocytes, the rate of fertilization, and the cleavage rate did not differ between the mifepristone group and the controls.

### Tubal environment and function

When treatment with mifepristone takes place just prior to ovulation, follicular rupture may occur. Mifepristone in high doses, due to its long half-life, may also affect tubal and uterine functions. The tubal microenvironment is probably of great importance to ensure normal embryo development, and stage-specific expression of receptors for various growth factors has been found on human embryos (Smotrich *et al.*, 1996). Too rapid or too slow tubal transport could also be expected to cause desynchronization between the embryo and the tube, and/or the blastocyst and the endometrium. Progesterone regulates tubal transport *in vitro*, as confirmed in a study by Mahmood *et al.* (1998). Cilia from the human Fallopian tube beat significantly slower after treatment with high doses of progesterone, an effect that could be reversed by mifepristone. Furthermore, animal studies have previously shown accelerated tubal egg transport after mifepristone treatment (Psychoyos and Prapas, 1987).

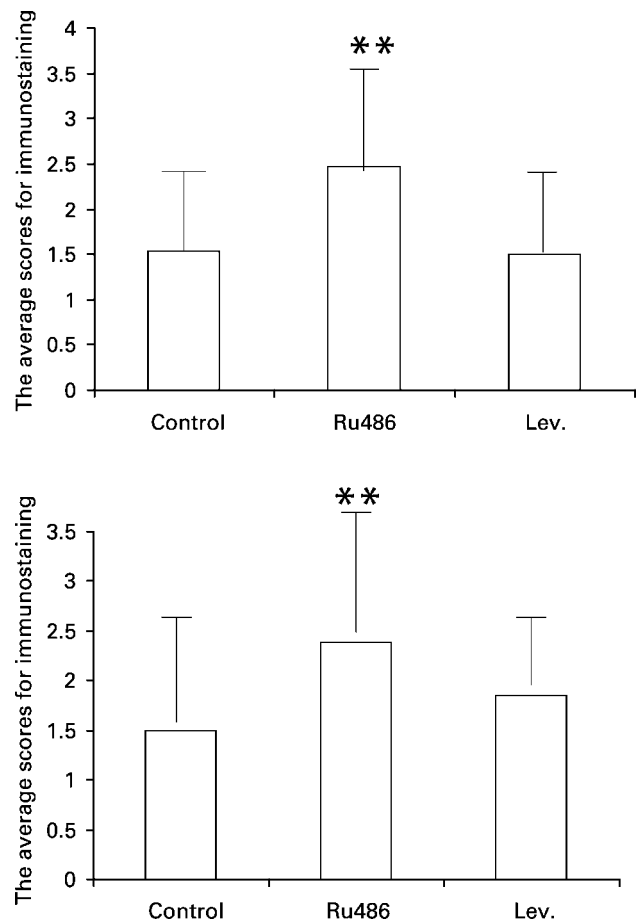
A spatially dependent expression of progesterone receptors has been shown in the human Fallopian tube (Christow *et al.*, 2002). Higher levels of receptors are being expressed in the isthmus region than the ampullar region of the tube on days LH + 4 to +6. Following the administration of 200 mg of mifepristone on day LH + 2, progesterone receptor concentration increased in epithelial and stromal cells. There was also an effect on estrogen receptor levels, although less pronounced and restricted to the epithelial cells (Figure 2).

The treatment with 0.75 mg of levonorgestrel twice with a 12 h interval did not affect the distribution of progesterone or estrogen receptors.

### Endometrial development and implantation

#### Pre-ovulatory treatment

A single dose of 10 mg of mifepristone administered ~2 days prior to ovulation inhibited or delayed the LH surge in all subjects (Marions *et al.*, 2002). The luteal phase levels of estrone- and pregnanediol-glucuronide were slightly decreased compared to control levels (Marions *et al.*, 2004). Two subjects showed

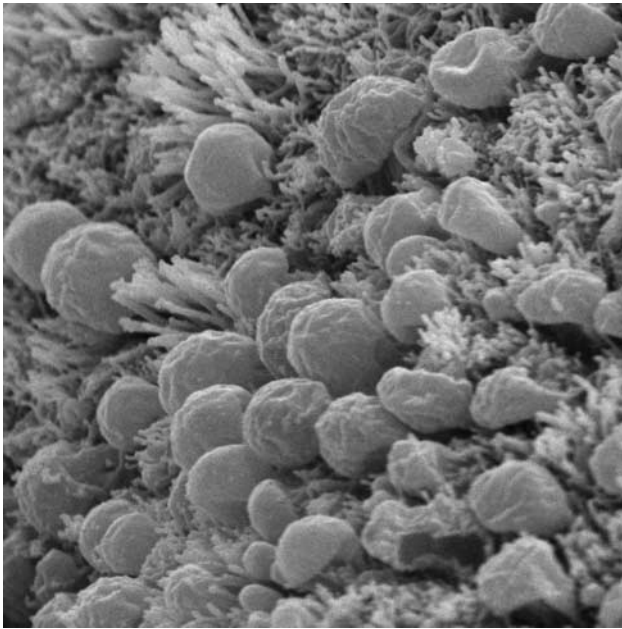


**Figure 2.** Immunostaining of (a) progesterone receptors (PR) and (b) estrogen receptors (ER) in the human Fallopian tube on day LH + 4 to +6 in controls and following treatment on day LH + 2. Treatment with 200 mg of mifepristone significantly increased expression of PR and ER. Treatment with levonorgestrel (0.75 mg twice) had no effect. Mean and SD of immunoscore.

a slight inhibition of endometrial development on cycle days LH + 6 to +8. The expression of the  $\beta 3$  integrin subunit in the glandular epithelial cells was decreased in two subjects. The expression of COX-1 and -2, integrin  $\alpha 4$ , progesterone receptors and DBA-lectin binding as well as pinopode development was the same as observed in control cycles (Figure 3).

In contrast, a higher dose of mifepristone given in the peri-ovulatory phase, even when too late to inhibit ovulation, affected endometrial development during the luteal phase. When a single dose of 200 mg of mifepristone was given at the time when LH just started to increase, ovulation occurred in five women and was delayed in two women. Endometrial development during the mid-luteal phase was assessed in six women (Brown *et al.*, 2003). Asynchrony between the endocrine patterns, and between the endometrial appearances, was described. There was a failure of normal secretory change, with absent or minimal vacuolation and an increased number of mitoses.

Treatment with levonorgestrel 0.75 mg twice, 12 h apart, on day LH-2 had no effect on the endometrial development during the mid-luteal phase at the expected time of endometrial receptivity and implantation (Marions *et al.*, 2002).



**Figure 3.** Pinopod formation in varying developing stages. Endometrial sample obtained on LH + 6 following mifepristone 10 mg on LH-2. Electron microscopy. Original magnification  $\times 200$ .

**Post-ovulatory treatment**

Treatment with a single dose of 200 mg mifepristone on day LH + 2 has been shown to be an effective contraceptive method (Gemzell Danielsson *et al.*, 1994; Hapangama *et al.*, 2001a) (Table II). Early luteal phase treatment causes changes in endometrial glandular apoptosis, secretory activity, expression of steroid receptors, especially progesterone receptors but also androgen and estrogen receptors, integrins and leukaemia inhibitory factor (LIF) at the expected time of implantation (Gemzell Danielsson *et al.*, 1997a, 1998; Marions *et al.*, 1998a; Critchley *et al.*, 1999; Slayden *et al.*, 2001). Mifepristone also affects calcitonin expression (Kumar *et al.*, 1998) as well as prostaglandin dehydrogenase (Cameron *et al.*, 1997). Furthermore, changes occur in the composition and amount of uterine fluid (Gemzell Danielsson and Hamberg, 1994). The normal menstrual rhythm remains undisturbed and serum levels of estradiol and progesterone remain essentially unchanged (Swahn *et al.*, 1990). Treatment with 5 mg mifepristone once a week with start on cycle day 2 did not inhibit ovulation but retarded or desynchronized endometrial development (Gemzell Danielsson *et al.*, 1996). An increase in progesterone receptor levels was observed as well as an impaired secretory activity. When an even lower

dose of 0.5 mg was administered daily for three cycles, all subjects ovulated and similar changes were observed in the endometrium although to a lesser degree than with the once-weekly regimen (Gemzell Danielsson *et al.*, 1997b). Both regimens have been shown to significantly impair fertility although not sufficient for contraceptive use (Marions *et al.*, 1998a, 1999).

When a single dose of 10 mg mifepristone was administered on day LH + 2, the observed effect on the endometrium was less pronounced than after treatment with 200 mg or repeated low doses (Marions *et al.*, 2002). Following 10 mg, the endometrium was slightly out of phase, while no obvious effect was seen on LIF and integrin expression or pinopod development. DBA lectin binding, reflecting endometrial secretory activity, was reduced in four of six subjects and down-regulation of progesterone receptors was inhibited in five of six subjects. A large number of factors have been suggested as markers of endometrial receptivity, but progesterone receptor concentration could be expected to be highly associated with successful implantation since many of the relevant local factors such as cytokines are progesterone-regulated. However, different regulatory mechanisms or pathways may be involved. In Bonnet monkeys treatment with onapristone in doses ranging from 2.5 to 10 mg every third day did not inhibit ovulation and had only a minor effect on endometrial morphology, but it was shown to be highly effective in inhibiting endometrial receptivity and implantation (Puri *et al.*, 2000). The lowest dose, 2.5 mg every third day, did not affect progesterone receptor expression, but reduced LIF and integrins. However, higher doses affected all markers (Table II).

Levonorgestrel (0.75 mg  $\times$  2) administered on day LH + 2 did not affect endometrial morphology or any studied markers of receptivity (Durand *et al.*, 2001; Marions *et al.*, 2002).

**Corpus luteum**

Down-regulation of progesterone receptor B (PR<sub>B</sub>) mRNA occurs in the mid-luteal phase corpus luteum (Ottander *et al.*, 2000). PR<sub>B</sub> mRNA levels were found to be 100–1000-fold lower than progesterone receptor A plus B (PR<sub>A/B</sub>) mRNA levels and were 46% lower in mid-luteal phase, compared to early and late luteal phase. Freshly obtained mid-luteal corpus luteum cells were cultured *in vitro* and media analysed for progesterone concentrations after treatment with hCG and mifepristone. Mifepristone did not alter progesterone synthesis *per se*, but when it was added in conjunction with hCG, a dose-dependent inhibitory response was seen, with a maximal 47% reduction in

**Table II.** Effects of antigestagens in various doses on potential markers of endometrial receptivity and contraceptive efficacy

| Species (antigestagen)      | Dose               | LIF, Integrin | PR              | Contraceptive efficacy |
|-----------------------------|--------------------|---------------|-----------------|------------------------|
| Human (mifepristone)        | 5 mg/week          | Decrease      | Slight increase | Low                    |
|                             | 0.5 mg daily       | Decrease      | No effect       | Low                    |
|                             | 200 mg on LH + 2   | Decrease      | Strong increase | High                   |
|                             | 10 mg on LH + 2    | No effect     | Increase        | Not studied            |
| Bonnet monkey (onapristone) | 2.5 mg/3rd day     | Decrease      | No effect       | High                   |
|                             | 5 or 10 mg/3rd day | Decrease      | Increase        | High                   |

progesterone output at a 10  $\mu\text{mol/l}$  mifepristone addition. The effect of mifepristone on early corpus luteum was not studied.

Administration of  $\geq 25$  mg of mifepristone during the mid- to late luteal phase results in shedding of the endometrium and vaginal bleeding within a few days of the treatment. The bleeding is probably induced by an effect of mifepristone on endometrial prostaglandin metabolism (Hapangama *et al.*, 2003). If premature menstruation is not accompanied by luteolysis in the mid-luteal phase ( $\sim 50\%$  of cases), the endometrial and ovarian cycles are desynchronized and a second bleeding episode occurs at the time of the expected menstruation (Schaison *et al.*, 1985; Garzo *et al.*, 1988; Swahn *et al.*, 1988). The manner in which antiprogestin induces luteolysis in certain situations is not precisely known, but could be indirect via withdrawal of LH support (Mais *et al.*, 1986) as shown by a reduction in amplitude and frequency of LH pulses and blunting of the pituitary LH response to GnRH (Schaison *et al.*, 1985; Garzo *et al.*, 1988). It may also depend on the age of the corpus luteum (Swahn *et al.*, 1988). Once-a-week treatment with 5 mg mifepristone did not inhibit ovulation and did not influence the length of the luteal phase (Gemzell Danielsson *et al.*, 1996).

The possibility of using the antiprogestin mifepristone for late luteal phase treatment or menstrual regulation has been evaluated in a number of studies (Ulmann, 1987; van Santen and Haspels, 1987; Dubois *et al.*, 1988; Lähteenmäki *et al.*, 1988). The overall failure rate per treatment cycle is  $\sim 5\%$  and per pregnant cycle 17% (for review, see Swahn *et al.*, 1996; Croxatto, 2003). Late luteal phase treatment with 200 mg mifepristone on the day prior to the expected menstruation, followed by a prostaglandin analogue 48 h later, was also shown to be ineffective as a contraceptive method (Swahn *et al.*, 1999).

## Discussion

Treatments with low dose mifepristone or levonorgestrel have emerged as effective, convenient and safe methods for emergency contraception. The contraceptive effect of 1.5 mg levonorgestrel or 10 mg of mifepristone involves blockade or delay of ovulation. The 'window of effect' for levonorgestrel seems to be rather narrow. It begins after selection of the dominant follicle, but before LH begins to rise. Levonorgestrel does not affect endometrial development or steroid receptor expression in the Fallopian tube. Animal studies confirm that levonorgestrel acts to block or delay ovulation but does not affect fertilization or implantation (Müller *et al.*, 2003). If the effect of EC is mainly to block the LH surge or to interfere with other processes involved in ovulation, is not clear and needs to be further studied.

The efficacy of levonorgestrel, 0.75 mg twice 12 h apart or a single dose of 1.5 mg, was shown to be equal to that of a single dose of 10 mg of mifepristone (von Hertzen *et al.*, 2002). Further analysis of the data shows that mifepristone seems to be slightly more effective in preventing pregnancy after one act of unprotected intercourse, while it is also more likely to postpone ovulation. Thus women with further acts of unprotected intercourse are put at higher risk of pregnancy.

A single dose of 10 mg mifepristone within 120 h of an unprotected intercourse has been shown to be as effective as doses of 50 or 600 mg but with significantly less side-effects. A great

advantage with the lower dose is that the effect on the menstrual cycle (WHO, 1999) and delay of the next menstruation is dose-dependent and less pronounced with this dose. A delay in the next menses may add to the worry about an unintended pregnancy. Furthermore, with the higher doses there is an increased risk of delayed ovulation which exposes the women to the risk of pregnancy should she have further acts of unprotected intercourse.

Treatment with 200 mg mifepristone on day LH + 2 changes the steroid receptor expression in the Fallopian tube, inhibits endometrial development, and effectively prevents implantation (Gemzell Danielsson *et al.*, 1993; Hapangama *et al.*, 2001). Low dose mifepristone (10 mg) administered after ovulation seems to have some effect on endometrial development and progesterone receptor expression although not as pronounced as the effect of the higher dose (i.e. 200 mg). The effect seems to be variable possibly reflecting individual sensitivity, or the 10 mg dose might be at the threshold of affecting the endometrium. Furthermore, treatment prior to ovulation did not significantly affect endometrial development in contrast to a single dose of 200 mg (Marions *et al.*, 2002; Brown *et al.*, 2003).

Daily low dose treatment with 0.5 mg mifepristone, had an effect on endometrial morphology similar to that of a 10 mg single dose, without influencing ovulation, and significantly reduced fertility (Marions *et al.*, 1999). However, 0.5 mg per day had a different effect on some proposed markers of endometrial receptivity. Low daily doses did not affect progesterone receptor expression, but significantly reduced LIF and integrin expression. In contrast, 10 mg on day LH + 2 affected progesterone receptor expression but had no effect on LIF and integrins.

In summary, available data from the studies in humans indicate that the contraceptive effect of 10 mg mifepristone used as a single dose for emergency contraception is mainly due to impaired ovarian function, either by blocking the LH surge or by postponing the surge rather than inhibiting the implantation. In contrast, higher doses affect both ovulation and implantation. It may seem surprising that doses ranging from 10 mg to 600 mg were reported to be equally effective. However, when the efficacy of 600 mg of mifepristone is further analysed and women who conceived after treatment are excluded, the data actually show that 600 mg is more effective than the lower doses (WHO, 1999). Thus, the mode of action of mifepristone, as well as efficacy, seems to be both dose and time dependent.

In conclusion, emergency contraception with 10 mg of mifepristone as a single dose or 1.5 mg of levonorgestrel acts mainly to inhibit or delay ovulation but does not prevent fertilization or implantation. Increased knowledge of the mechanism of action could hopefully increase the acceptability and thus availability of these methods, to offer women a chance to prevent an unwanted pregnancy and thus reduce the numbers of induced abortions.

## Acknowledgement

We are grateful to Associate Professor Sten Cekan for help in the editing and preparation of this article. The studies from the Karolinska Hospital referred to in the article were supported by UNDP/UNFPA/WHO/World Bank Special Programme of Research

Development and Research Training in Human Reproduction, World Health Organization, Geneva, Switzerland, and the Swedish Medical Research Council (nos. 05696, 05170 and 0855), The Knut and Alice Wallenberg Foundation, the Karolinska Institute Research Funds and Professor Sune Bergström, Karolinska Institute.

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*Submitted on December 12, 2003; resubmitted on February 20, 2004; accepted on April 8, 2004*