Antiprogesterone RU 486 — a Drug for Non-Surgical Abortion

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RU 486 is the first steroidal antiprogesterone in clinical use. It acts by binding to progesterone receptor, thus blocking the effects of progesterone at the uterine level, and provoking endometrial necrosis and shedding. RU 486 can, therefore, be used to interrupt early human pregnancy. In pregnancies of up to 7—8 weeks duration, the rate of complete abortions with RU 486 has ranged from 50 % to 90 %. The success rate can, however, be augmented up to 95 %—100 % by combining RU 486 with a low dose prostaglandin. RU 486 induced abortion has been well tolerated by women and highly acceptable to them. The bleeding starts 2—3 days after RU 486 administration lasting for 12—14 days. Possible clinical uses of RU 486 include induction of menstruation, late post-coital contraception, induction of labour after intrauterine fetal death, preoperative cervical ripening and treatment of progesterone receptor positive mammary tumours. When administered in the follicular phase of the cycle, RU 486 inhibits follicular development. In addition, the antiglucocorticoid properties of RU 486 have been used in symptomatic treatment of hypercortisolemia of Cushings disease. The pharmacokinetics of RU 486 are characterised by high micromolar serum concentrations, long half-life of 26—48 hours and substantial metabolism after oral administration. Although effective and well tolerated, RU 486 has aroused great moral controversy, which is currently hampering furter testing and distribution of the drug. So far RU 486 has been accepted for termination of pregnancy in France and in the Peoples Republic of China, to be used with prostaglandins and under strict medical surveillance.

Key words: RU 486; mifepristone; endocrine effects; pharmacokinetics; clinical use.

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Introduction

Estimates of pregnancy terminations in the world vary between 50 to 60 million annually, whereas the annual increase in population is approximately 90 millions (1). Legal abortions are also needed in developed countries because accidental pregnancies occur, no matter how effective family planning services are. In Finland, where contraception is easily available, the annual number of abortions exceeds 13 000 (2). Safe, effective, discreet and less traumatizing methods of termination of unwanted pregnancy are needed. Since the discovery of the indispensable role of progesterone hormone in the maintenance of early human pregnancy (3), one of the main goals in contraceptive research has been directed towards antagonising this progesterone action, thus terminating early pregnancy by a non-surgical method. Specific antagonism of progesterone can be achieved in two different ways: by inhibiting synthesis of progesterone, or by interfering with the interaction of progesterone with its intranuclear receptor protein in target cell. Both strategies are being currently tested.

RU 486 (mifepristone), the first progesterone and glucocorticoid antagonist at the receptor level was introduced in 1981 (4, 5). Since then, rapid progress has occurred in evaluating clinical applications of RU 486. More than 10 000 women have been enrolled in studies to evaluate of RU 486-induced termination of early pregnancy (6); several of these have been conducted under the supervision of the World Health Organization (WHO) and The Population Council.

Development of Antiprogesterone

Purification of progesterone (pro-gestare) from porcine corpus luteum, and the understanding of its biologi-

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cal importance in the maintenance of pregnancy in rabbits date back to 1930s (7, 8). Conclusive evidence on the indispensability of progesterone in the maintenance of early human pregnancy was not, however, presented until 1972 (3). Thus, antagonism of progesterone might be used for termination of an unwanted early human pregnancy. Various approaches have been tried: immunization against progesterone, inhibition of progesterone synthesis and biological antagonism by administring prostaglandins (9—11). Of these methods, only prostaglandin therapy has clinical significance in the termination of early pregnancy, but it is complicated by a high incidence side effects (11). Inhibition of synthesis of progesterone by Epostane, an inhibitor of 3β-hydroxy steroid dehydrogenase enzyme system, is being currently tested with a successrate of 84 % (12).

In target cells, the effects of agonist steroid hormones are mediated by intracellular receptor proteins, which characteristically bind steroids of their class with high affinity and specificity. Steroid hormones thus activate their receptors, which further bind to chromatin and regulate gene transcription (13). Studies by Teutsch and his co-workers (14) have shown that the structure of both progesterone and glucocorticoid receptors include a hydrophobic region capable of accepting large hydrophobic substituents in the 11β-position of the steroid molecule. This discovery, together with knowledge of the properties of two important compounds in steroid biochemistry, tamoxifen and norethindrone, led to the introduction of RU 486 (Fig. 1), the first specific progesterone and glucocorticoid receptor antagonist used in clinical work (4, 5).

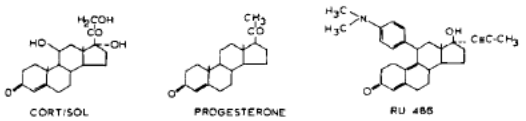

Figure 1. Molecular structures of progesterone, cortisol and RU 486.

Endocrine Effecs of RU 486

Mechanism of Action of RU 486 at the Receptor Level

RU 486 binds with high affinity to nearly all mammalian progesterone receptors investigated (15, 16). To the human progesterone receptor, RU 486 has an affinity more than twice as great as progesterone (17). The antiprogesterone effect of RU 486 is mediated via erroneous binding of activated RU 486-progesterone receptor complexes to chromatin (18, 19). RU 486 has a four times greater affinity to the human glucocorticoid receptor than DXM, a potent synthetic glucocorticoid (17). In contrast to the antiprogesterone action of RU 486, the antiglucocorticoid action is mediated by maintaining the RU 486-glucocorticoid receptor complexes in an unactivated state, which are then unable to bind to chromatin (20, 21).

Effects on the Hypothalamus-Hypophysis

Early studies by Herrmann et al. (15) showed that in the midluteal phase of the cycle, RU 486 (50 mg × 4d) lowered the basal levels of gonadotrophins, and this was accompanied by falls in the concentrations of serum estradiol and progesterone. Further studies in the luteal phase have shown that suppression of gonadotropin secretion by RU 486 was dose dependent; and that both the basal levels, and pulse amplitude of luteinizing hormone (LH) secretion were lowered (22). The effect of RU 486 on the pulse frequency of gonadotropin secretion is controversial: Schaison et al. (22) showed that the pulse frequency of LH increased, whereas in studies by Garzo et al. (23) RU 486 either had no effect, or prolonged the frequency of LH secretion depending on the stage of the luteal phase. In addition, RU 486 impaired the pituitary responses of LH to exogenous gonadotropin releasing hormone (GnRH) both *in vitro* (24) and *in vivo* (23). Hence, RU 486 has distinctly different effects on pituitary hormone secretion than progestins, which reduce LH pulse frequency and augment pulse amplitude (25).

Administration of RU 486 in the late follicular phase has been reported to reduce only slightly the basal levels of gonadotropins, LH pulse amplitude and frequency being unaffected. The midcycle LH/FSH-surge was, however inhibited by the treatment (26). In humans, the RU 486-attenuated midcycle gonadotropin surge is most likely caused by the significant reduction of ovarian estradiol production, and thus lack of positive feedback on the hypophysis and hypothalamus (26, 27).

Effects on the Ovaries

In addition to induction of uterine bleeding by direct action on the endometrium, RU 486 has a dose dependent luteolytic effect, which is independent of the concomitant gonadotropin levels (22, 28). Thus, after administration of RU 486 in the luteal phase, two distinct endocrine responses can be observed: RU 486 induced luteolysis with a single period of bleeding resembling normal menstruation, accompanied by declining serum levels of estradiol and progesterone. When RU 486 causes only partial luteal regression, the serum levels of estradiol and progesterone remain unaffected, and after RU 486-induced light uterine bleeding, a second bleeding occurs at the time of expected menstruation (23, 29).

In humans administration of RU 486 in the follicular phase of the cycle inhibits augmentation of ovarian estradiol production (26, 27, 30). Analogously with progestins, RU 486 lowers the amount of basal and hCG-stimulated estradiol and progesterone secretion by human granulosa cells *in vitro* (31).

Effects on the Uterus

RU 486 induces uterine bleeding by direct action on the endometrium (Fig. 2). In monkeys, RU 486-induced endometrial shedding occurs homogenously and quite deeply throughout the uterus (32). In the absence of progesterone, RU 486 has a weak progestomimetic effect on the human endometrium, but when ad-

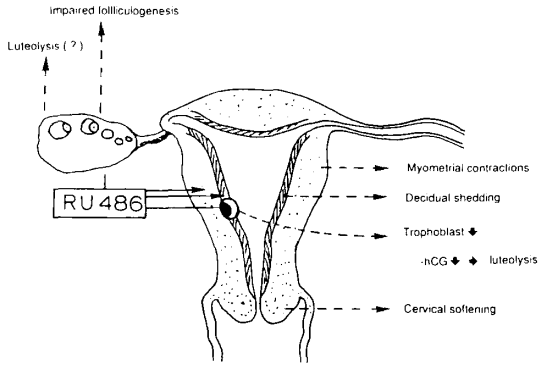

Figure 2. Schematic presentation of the principal mechanisms of action of RU 486 at the uterine and ovarian level.

ministered with progesterone, RU 486 behaves as a pure angatonist (16).

Throughout pregnancy a continuous supply of progesterone maintain the human uterus in a quiescent stage by suppressing prostaglandin (PG) synthesis (33). RU 486 stimulates the synthesis of PGs of $F_{2\alpha}$ and E_2 series by stromal cells of endometrium and glandular cells of decidua *in vitro* (34, 35). In early pregnancy, exogenous PGs, when administered 1.5—3 days after commencement of RU 486 treatment, greatly stimulate the frequency and amplitude of uterine contractions (36). The time lag between the start of RU 486 administration and the increased sensitivity of uterus to PGs accords well with the delay in the start of uterine bleeding and the lack of histological changes in endometrium at 1.5 days after intake of RU 486 (23). Thus, these studies show that at the endometrial and/or myometrial level the primary effects of RU 486 are mediated through increased concentrations of PGs.

Effects on the Placenta

In cell cultures of first and third trimester placentas RU 486 impairs the synthesis of the placental hormones and proteins human chorionic gonadotrophin (hCG), human placental lactogen (hPL), progesterone and pregnancy-associated plasma protein-A (PAPP-A) (37, 38). After administration of RU 486, serum levels of placental protein 12 (PP12) fell rapidly in patients requiring termination of pregnancy (39). *In vivo,* a decline in circulating levels of these hormones by RU 486 might potentiate the abortifacient properties of RU 486 (37, 38).

Effects on the Pituitary-Adrenal -Axis

RU 486 increases the pituitary secretion of adrenocorticotrophic hormone (ACTH) and other proopiomelanocortin-derived peptides in a dose dependent manner, thereby also increasing the secretion of cortisol (40, 41). In all species investigated the antiglucocorticoid effects of RU 486 are seen only after high oral doses of RU 486 (42, 43). In dogs, high doses of RU 486 also increased serum concentrations of aldosterone, but this was associated only with mild normosmolar hypervolemia (43). Analogous to its partial progestomimetic action in humans, RU 486 suppresses the pituitary secretion of ACTH in response to exogenous corticotropin releasing hormone (CRH), suggesting a weak glucocorticoid agonist activity of RU 486 (16, 44). The glucocorticoid agonist effect of RU 486 was not, however, sufficient to support life in adrenalectomized monkeys (45).

Antiproliferative Effect on Cancer Cells

RU 486 is cytotoxic against progesterone receptor positive breast cancer cell lines *in vitro* (46, 47). This property of RU 486 is mediated via a progesterone receptor and is independent of concomitant estrogen levels (48), but the precise mechanism of cytotoxity remain unclear. The growth inhibiting property of RU 486 is a progestin like effect, although RU 486 does not stimulate the synthesis of progestin induced proteins or insulin binding sites, indicating pure antiprogesterone action (46, 47). Thus, as regards breast cancer cells, the cytotoxic effects of RU 486 reflect the dual agonist-antagonist nature of RU 486. In endometrial cancer cells RU 486 shows a distinctly different behaviour, for *in vitro,* RU 486 reverses the progestin induced growth inhibition of these cells (49).

Clinical Use of RU 486

Termination of Unwanted Pregnancy with RU 486

Since the introduction of RU 486, the main focus of clinical research has been directed towards terminating unwanted pregnancies by blocking the effect of progesterone. RU 486 induces decidual necrosis and softening of the cervix, which elicit uterine bleeding, whereas the trophoplast remains histologically unaltered (50). Expulsion of the trophoplast, leading to declining serum hCG concentrations, causes subsequent lyteolysis, although RU 486 itself seems to have some luteolytic activity (Fig. 2) (22, 28).

Table 1 summaries the main clinical studies on termination of early pregnancy with RU 486. A common feature in these studies has been the lack of correlation between the doses of RU 486 used, and the clinical outcome. The studies by Haspels (52) and Elia (55) suggest that the shorter the duration of the pregnancy, the better the clinical outcome. In pregnancies shorter than seven weeks duration, the gestational length did not affect the clinical outcome (56—58, 60).

The reasons why some women fail to respond to RU 486 therapy are not known. However, uterine bleeding and thus complete or incomplete abortion seems to occur in almost all women. Classification of pretreatment parameters in patients who have had complete or incomplete abortions, has shown that the only predictor of successful clinical outcome is a low value of serum hCG, which has a sensitivity of 93 % (58). By accepting only patients with pretreatment β-hCG values below 18 000 U/l for their study, Couzinet et al. (54) reported high success rates of 82—88 %.

Table 1. Pregnancy termination with RU 486.

Investigators	Patients*	RU 486	Outcome†
Herrmann et al. (15)	Imp 6—8 w	200 mg × 4d	9/11 (82 %)
Kovacs et al. (51)	Imp ≤ 6 w	I. 25 mg bid × 4d	12/19 (63 %)
		II. 50 mg bid × 4d	5/10 (50 %)
		III. 100 mg bid × 4d	5/8 (63 %)
Haspels (52)	Imp < 8 w	I. 100 mg bid × 4d	9/12 (75 %)
		II. 200 mg × 4d	10/12 (83 %)
	Imp 8—10 w	200 mg × 4d	3/9 (33 %)
Cameron et al. (53)	Imp < 8 w	150 mg × 4d	12/20 (60 %)
Couzinet et al. (54)	Imp < 5 4/7 w + β-hCG < 18 000 U/l	I. 50 mg bid × 4d	28/34 (82 %)
		II 50 mg × III × 4d	23/26 (88 %)
		III. 400 mg × 2d	34/49 (85 %)
Elia (55)	Imp < 5 w		93/105 (89 %)
	Imp 5—6 w	Single dose 600 mg	193/257 (75 %)
	Imp > 6 w		41/71 (58 %)
Shoupe et al. (56)	Imp ≤ 7 w	I. 50 mg bid × 7d	34/47 (72 %)
		II. 100 mg bid × 4d	1/5 (20 %)
		III. 200 mg bid × 4d	0/5
Mishell et al. (57)	Imp ≤ 7 w	I. 25 mg bid × 7d	15/30 (50 %)
		II. 50 mg bid × 7d	48/66 (73 %)
Birgerson and Odlind (58)	Imp < 7 w	I. 10 mg bid × 7d	35/48 (73 %)
		II. 25 mg bid × 7d	34/52 (66 %)
		III. 50 mg bid × 7d	34/53 (64 %)
Grimes et al. (59)	Imp ≤ 7 w	Single dose 600 mg	44/49 (90 %)
Ylikorkala et al. (60)	Imp ≤ 6 1/7 w	Single dose 600 mg	36/50 (72 %)

* Patients: Criteria for the maximum duration of pregnancy accepted for the study (Imp = last menstrual period, i.e. duration of pregnancy), in addition to verified intrauterine pregnancy.
† Outcome: Frequency of complete abortions (uterine bleeding subsequent to RU 486; low β-hCG and empty uterine cavity by ultra-sonographic or bimanual examination on re-examination). Number of complete abortions/number of women treated, (percentage of complete abortions).

Patterns of Bleeding Following RU 486 Treatment

After administration of various doses of RU 486 the patterns of bleeding are remarkably similar: in women with complete abortions bleeding starts 2—3 days after the start of RU 486 administration and lasts for 12—14 days thereafter (56—58). The products of conception are expelled approximately one day after the start of bleeding (58). With the lowest doses of RU 486 tested for pregnancy termination, the bleeding starts somewhat later (56, 58). When abortion is incomplete, bleeding tends to start later and its duration is shorter (56, 58).

Acceptance of RU 486 Treatment

Only two papers describe the subjective acceptance of RU 486-induced termination of pregnancy. Bigerson and Odlind (61) report that 81 %—88 % of their patients were satisfied and willing to repeat the treatment should they ever want an abortion again. In another study most patients tended to describe their experiences as "not unpleasant" and "not as bad as I expected" (52). Positive comments accord favourably with the rates of complete abortions.

Side Effects Associated with RU 486

The frequency of reported side effects associated with RU 486-induced abortion vary considerably between studies. Side effects such as mild uterine pain, fatigue, nausea and vomiting have been reported (51, 52, 58), but the distiction between these and the usual symptoms of early pregnancy and abortion is difficult. Weakness has been reported by 22 % and 25 %, and nausea by 24 % and 47 % of the patients (54, 57).

A mild fall in blood hemoglobin concentration occurs subsequent to RU 486 treatment (58, 62). Heavy uterine bleeding complicated RU 486 induced abortions in 18 % and 56 % of the patients, respectively, in the studies by Couzinet et al. (54) and Mishell et al. (57). In addition, some authors have reported occasional patients suffering from severe bleeding requiring blood transfusions (15, 51, 52).

Termination of Pregnancy by Combination of RU 486 and Prostaglandins

In vitro studies have shown that RU 486 induces synthesis of prostaglandins (PG) in glandular cells of the decidua (35). Hence the oxytocic action of RU 486 might be potentiated and better success rates achieved by administration of additional PGs. In practice, the addition of subtherapeutic doses of PGs to RU 486 treatment increases the frequency of complete abortions to between 90 % and 100 %; the results of these studies are summarized in Table 2.

The patterns of bleeding, side effects and return of menstruation were similar between the "RU 486 only" and the "RU 486 + PG" -groups (53). When compared

Table 2. Pregnancy termination with RU 486 combined with prostaglandin analogs.

Investigators	Patients*	RU 486	Outcome†
Swahn et al. (63)	Imp≤7 w	I. 25 mg bid × 4d/6d + 0.25 mg PGE_2-analog i.m.‡	9/9 (100 %)
		II. 25 mg × IV × 4d + 0.25 mg PGE_2-analog i.m.	7/7 (100 %)
Cameron et al. (53)	Imp<8 w	I 150 mg × 4d + 1 mg PGE_1-vaginal pessary§	18/19 (95 %)
		II. 150 mg × 4d + 2 mg PGE_1-vaginal pessary	5/5 (100 %)
Rodger and Baird (64)	Imp<8 w	I. 150 mg × 4d + 1 mg PGE_1-vaginal pessary§	19/20 (95 %)
		II. single dose 500 mg + 0.5 mg PGE_1-vaginal pessary	29/30 (97 %)
		III. single dose 400 mg + 0.5 mg PGE_1-vaginal pessary	27/30 (90 %)
		IV. single dose 600 mg + 0.5 mg PGE_1-vaginal pessary	20/20 (100 %)
Ji et al. (65)	Imp≤7 w	single dose 600 mg + 1.0 mg $PGF_{2\alpha}$-vaginal supp.II	136/160 (87 %)
Rodger et al. (66)	Imp<8 w	I. single dose 600 mg + 0.5 mg PGE_1-vaginal pessary§	59/60 (98 %)
		II. single dose 600 mg + 1.0 mg PGE_1-vaginal pessary	60/60 (100 %)

* Patients: Criteria for the maximum duration of pregnancy accepted for the study (Imp = last menstrual period, i.e. duration of pregnancy), in addition to verified intrauterine pregnancy.
† Outcome: Frequency of complete abortions (low β-hCG and empty uterine cavity by ultra-sonographic or bimanual examination on re-examination). Number of complete abortions/number of women treated, (precentage of complete abortions).
‡ 16-phenoxy-tetranor-PGE_2 methyl sylfonylamine (Schering AG, Berlin).
§ 16, 16-dimethyl-trans-Δ^2-PGE_1 methylester (Gemeprost).
II 15-methyl-$PGF_{2\alpha}$-methyl ester (PGO5).

to treatment with high doses of PGs alone, the combination therapy of "RU 486 + subtherapeutic PG" were equally effective, but with a significantly lower incidence of gastrointestinal side effects (67). In termination of second trimester pregnancies (i.e. 16—18 weeks), addition of RU 486 into extra-amniotic PG therapy significantly reduced both the induction to abortion interval and the total dose of PG needed (68).

Other Possible Uses of RU 486 in Gynaecology and Obstetrics

RU 486 in Induction of Menstruation, and in Late Postcoital Contraception

RU 486 induces uterine bleeding by direct action on progesterone primed endometrium when administered in the mid- or late-luteal phase of the cycle (15, 22, 28). The bleeding starts 2—3 days after starting RU 486 and corresponds to regular menstruation both in duration and in amount (22). In addition, administration of 100 mg × 4d of RU 486 during the late luteal phase in three consequtive cycles was well tolerated and resulted in regular and endocrinologically normal cycles (69).

These results have encouraged the use of RU 486 as a late postcoital contraceptive or an inducer of once a month menstruations. Preliminary clinical experience, however, has been somewhat disappointing: van Santen and Haspels (70) reported one pregnancy among 62 patients requesting postcoital contraception. Lähteenmäki et al. (71) studied the late postcoital use of RU 486 in 30 women following unprotected intercourse around the midcycle. A single dose of 600 mg of RU 486 was administered as the time of expected menstruation. In 60 % of these patients pregnancy was confirmed by raised serum hCG concentrations; pregnancy continued in 3.3 % of patients despite of RU 486 treatment. An additional complication was a lengthening of the subsequent cycle by four days, which may limit regular once a month use of RU 486. Van Santen and Haspels (72) studied the use of RU 486 (100 mg × 4d) as a monthly, late luteal phase contraceptive: among the 24 cycles studied three conceptions occurred, two of which continued despite RU 486 treatment.

RU 486 in Fetal Death and Extrauterine Pregnancy

RU 486 has been used in induction of labour in late pregnancy after intrauterine fetal death (73). In addition, two groups of investigators have speculated on the possible use of RU 486 in the extraction of an extrauterine pregnancy. Paris et al. (74) concluded that pretreatment with RU 486 facilitates the extraction of the fetus by laparoscopy, whereas in a study by Keningsberg et al. (75), RU 486 was ineffective in treating of residual ectopic trophoplastic tissue.

Follicular Phase Administration of RU 486

Follicular phase administration of RU 486, commencing either a few days before the expected midcycle gonadotropin surge (26, 27, 76) or from the start of the

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