Clinical pharmacology of RU 486—an antiprogestin and antiglucocorticoid

Irving M. Spitz, MD and CW Bardin, MD

Center for Biomedical Research, The Population Council, 1230 York Avenue, New York, NY 10021

Keywords: RU 486; mifepristone; antiglucocorticoid; antiprogestin; abortion induction; prostaglandins; ovulation inhibition; menses induction; postcoital contraception; cervical dilatation.

I. Background

Over the last few years, several reviews have focussed on various but limited aspects of antiprogestins in general and RU 486 in particular.[1-4] The present review attempts a comprehensive evaluation of the physiology and current clinical uses of RU 486.

Progesterone plays a critical role in mammalian reproduction in that it is essential for the initiation and maintenance of pregnancy. Following the discovery of the progesterone receptor,[5] it was recognized that a progesterone receptor antagonist would be a significant advance in contraceptive technology if it could induce menstruation when used in the luteal phase (once-a-month pill), prevent implantation (morning after pill), and promote abortion in early pregnancy. Furthermore, since progesterone facilitates the action of estradiol in inducing the LH surge prior to ovulation,[6] a contraceptive action of a progesterone antagonist was also contemplated.

The search for such an antiprogesterone extended over more than a decade. The eventual discovery was fortuitous since the scientific team was in fact looking for a glucocorticoid antagonist. (For the interesting story behind the early studies, see reference 1.) In 1981, Philibert and coworkers[7] from Roussel-Uclaf reported the first highly effective progesterone antagonist designated RU 38486, subsequently abbreviated to RU 486

Submitted for publication April 1, 1993; accepted for publication September 13, 1993.
Address correspondence to: Irving M. Spitz, MD, The Population Council, 1230 York Avenue, New York, NY 10021

and currently known by the generic name mifepristone. The original studies showed that RU 486 displayed a relative binding activity five times that of progesterone to the rabbit uterine progestin receptor and three times greater than dexamethasone to the rat thymus glucocorticoid receptor. Its relative binding affinity for the rat prostate androgen receptor was only 25% that of testosterone, and there was no binding to the mouse uterine estrogen or rat kidney mineralocorticoid receptors. Further biological tests in animals showed that the compound behaved as a potent antagonist for progestins and glucocorticoids.[8] The affinity of RU 486 for both the progestin and glucocorticoid receptor was not unexpected in view of the numerous biological studies showing that progestins have weak glucocorticoid activity and vice versa. Moreover, the predicted amino acid sequence of the glucocorticoid and mineralocorticoid receptor steroid binding domains shows a greater similarity to that of the progesterone receptor than to any of the other receptors in this family.[9]

II. Structure of RU 486 and Other Antiprogestins

RU 486, 11-[4-(dimethylamino)phenyl-17-hydroxy-17-(1-propynyl)-(11β, 17β)-estra-4,9-dien-3-one, is a derivative of norethindrone that lacks the C19 methyl group and the 2-carbon side chain at C17 of progesterone and glucocorticoids (Figure 1). RU 486 differs from norethindrone due to a 4-(dimethylamino) phenyl group at the 11β position and a 1-propynyl chain

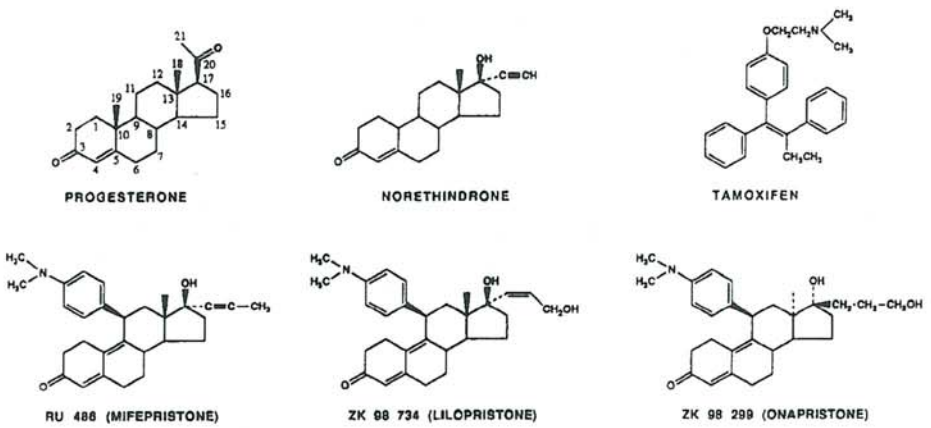

FIGURE 1. Chemical structure of progesterone, norethindrone (17-hydroxy-[17α]-19-norpregn-4-en-20-yn-3-one), tamoxifen ((*Z*)-2-[4-(1,2-dipheny-1-butenyl)phenoxy]-N,N-dimethylethanamine), RU 486 (11-[4-dimethylamino)phenyl] -17-hydroxy-17-[1-propynyl]-[11β,17β]-estra-4,9-dien-3-one), ZK 98734 (11-[4-(dimethylamino)-phenyl]-17-hydroxy-17-[3-hydroxy-1-propenyl]- [11β, 17β, 17α(*Z*)]-estra-4,9-dien-3-one) and ZK 98299 11-[4-(dimethylamino)phenyl]-17-hydroxy-17-[3-hydroxypropyl-[11β, 13α, 17α]-estra-4,9-dien-3-one).

at the 17α position. The conjugated C9-C10 double bond in RU 486 should also be noted. The 17α substitution probably imparts higher binding affinity for the receptor. By analogy with antiestrogens, it is likely that the substitution at the 11β position is responsible for its antagonistic action by inducing or stabilizing a biologically inert receptor conformation.[2,10]

Numerous additional antiprogestins have been synthesized and many are undergoing preliminary evaluation.[11] ZK 98734 (lilopristone) has a cis (*Z*)-configuration in the 3-hydroxy-1-propenyl side chain at the 17α position and is structurally very similar to RU 486 (Figure 1). The two-dimensional structure of ZK 98299 (onapristone) is similar to RU 486 and ZK 98734 (Figure 1). However, ZK 98299 has a different molecular shape due to configurational inversions at the C13 and C17 positions.[11]

ZK 98734 and ZK 98299 also bind with high affinity to glucocorticoid and progesterone receptors. Although there are some species differences, their antiprogestational and antiglucocorticoid activities are comparable.[11] ZK 98299 exerts stronger synergistic effects when given with prostaglandins and oxytocin, and it has the most potent effect on the cervix in the guinea pig.[11] ZK 98734 and ZK 98299 have less antiglucocorticoid action than RU 486.[11] At the present time, only RU 486 has been extensively studied in humans and, as a consequence, will be the major focus of this review.

III. Mechanism of Action

The action of progesterone in target tissues is mediated by the progesterone receptor (PR), which like the other members of this nuclear receptor family is a ligand-activated transcription factor with domains for DNA binding, hormone binding, and transactivation.[9] The PR of most species has a large hydrophobic pocket which can accommodate substitutions at position 11β like those on RU 486.[10] Spontaneous mutations of the progesterone receptor have been difficult to identify since the phenotype of women with such a mutation would be unexplained sterility and the defect could not be inherited. Therefore, an analysis of how the amino acid sequence of the receptor relates to progesterone binding must depend upon site-directed mutations made in the laboratory. Nonetheless, an experiment of nature showed that a glycine in the hormone binding domain of the human PR at position 722 (Gly^{722}) and at the comparable position of the PR of most other species is critical for RU 486 binding and action (Figure 2).[12] The hamster and the chicken PR that have a cysteine residue at this position[12] bind progesterone but not RU 486. These species are, therefore, insensitive to this antagonist.[2] Substitution of this cysteine by glycine converts the hormone binding domain of the chicken PR to one that binds RU 486 and facilitates the antagonistic action of this compound.[12] Substitution of Gly^{722} with cysteine in the

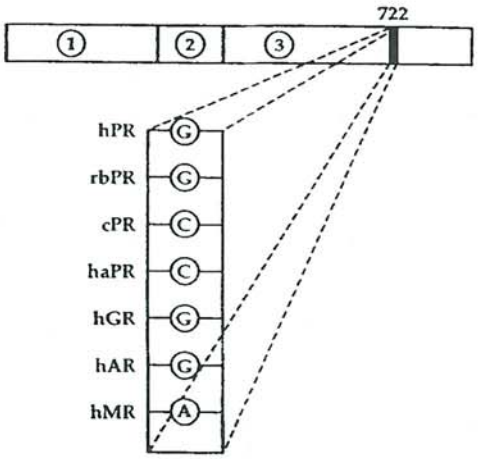

FIGURE 2. Schematic diagram of the primary structure of the human progesterone receptor (hPR) showing: (1) transactivation domain; (2) DNA binding domain; and (3) hormone binding domain. The amino acid glycine (Gly^{722}) in the hormone binding domain is critical for RU 486 (but not progesterone) binding. Amino acids corresponding to Gly^{722} in the rabbit PR (rbPR), chicken PR (cPR), hamster PR (haPR), human glucocorticoid receptor (hGR), human androgen receptor (hAR), and human mineralocorticoid receptor (hMR) are also shown. Receptors with glycine at this position bind and respond to RU 486; those with other amino acids do not. G = glycine; C = cysteine; A = alanine.

human PR generates a receptor that behaves like the chicken and hamster PRs. Introduction of the same cysteine substitution at the corresponding position in the human glucocorticoid receptor resulted in a loss of binding not only to RU 486 but also to dexamethasone.[12] In fact, the human glucocorticoid and androgen receptors, which bind RU 486, also have a glycine in this corresponding position (Figure 2). Because glycine is the only amino acid without a side chain, these results suggest that Gly^{722} in the human PR is at a critical position in the 11β-pocket and the presence of amino acid side chains in this position may sterically impede RU 486 binding.[12] The precise molecular mechanisms whereby progesterone and RU 486 produce their agonistic and antagonistic activities, respectively, via the PR are under active investigation.[13,14] The most recent in vivo and in vitro data support the actions summarized in Figure 3. Progesterone and other progestins produce a dramatic change in conformation of the PR that is associated with transforming (activating) PR from a non-DNA binding form to a form that will bind to DNA. This transformation is accompanied by a loss of associated heat-shock proteins and dimerization. The activated receptor dimer can bind to progesterone response elements in the promoter region of progesterone-responsive genes and, in the pres-

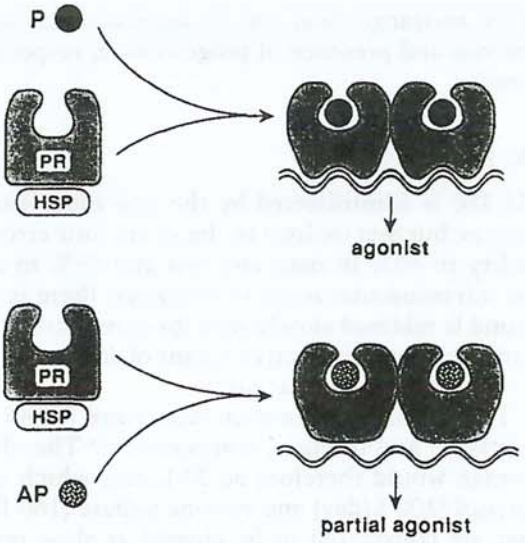

FIGURE 3. Proposed mechanisms of action of progesterone (P) and the antiprogestin (AP) RU 486. In the absence of ligand, the progesterone receptor (PR) is associated with heat-shock proteins (HSP). Association of PR with either P or AP induces different conformational changes in PR, both of which result in dissociation of HSP, dimerization of PR, and association of PR with the specific progesterone response elements in the promoter regions of progesterone-responsive genes. When bound, the P-PR complex is transcriptionally active resulting in agonistic effects (upper diagram). In the absence of P, the AP-PR complex behaves as a partial P agonist (lower diagram). The AP-PR complex is inactive (antagonistic) in the presence of P. The mechanism by which RU 486 can be antagonistic and agonistic in the presence and absence of progesterone is not known. One possibility is that agonistic effects result when both binding sites on the receptor dimer bind the antiprogestin and that antagonistic effects result when one monomer binds antiprogestin and the other binds progesterone (not shown).

ence of other nuclear transcription factors, increases the rate of transcription of these genes, thus producing agonistic effects at the cellular and tissue levels (Figure 3). When RU 486 binds to the inactive progesterone receptor, it induces an equally dramatic change in receptor conformation, loss of heat-shock proteins, and dimerization. The steroid receptor antagonist complex also will bind tightly to progesterone response elements, but these DNA bound receptors are transcriptionally inactive if progesterone is present. This is the basis for the abortifacient action of antiprogestins. However, in the absence of progesterone, the steroid receptor RU 486 complex may be transcriptionally active on some genes and RU 486 thus acts as a "partial agonist". This term is used because RU 486 does not duplicate all of the actions of progestins (see below). It is possible that antineoplastic effects of antiprogestins relate to these agonistic effects. The precise molecular mechanism whereby RU 486 (and possibly

other antiprogestins) can be agonistic and antagonistic on cells in the absence and presence of progesterone, respectively, is not known at this time.

IV. Pharmacology

RU 486 is administered by the oral route and is readily absorbed in all species, but metabolism in the splanchnic circulation reduces its bioavailability to 40% in man and rats and 15% in monkeys.[15] When given by the intramuscular route to monkeys, there is a depot effect and the compound is released slowly into the circulation.[16] Vaginal administration in humans is not an effective means of delivering the doses usually necessary for pregnancy termination.[17]

The metabolic clearance rates were 72, 36, and 0.55 L/kg/day in rats, monkeys, and humans, respectively.[15] The clearance rate for an average woman would therefore be 30 L/day, which is considerably slower than cortisol (200 L/day) and estrone sulfate (160 L/day), two natural steroids that are considered to be cleared at slow rates. The differences in the clearance rates between man and animals result in part from an α_1 acid glycoprotein, orosomucoid, in serum that binds RU 486 in humans (kD ~1 μM) but not in other species.[2,18] RU 486 does not bind to cortisol binding globulin or sex-steroid binding globulin.[2]

In women, following oral administration of single doses ranging from 50–800 mg, serum RU 486 levels reached a maximum in 1 hour. Depending on the dose administered, the pharmacokinetics displayed two distinct patterns.[19] After a low dose (50 mg), the disappearance of RU 486 follows first order kinetics with a half-life of 20–25 hours (Figure 4). After ingestion of doses of 100–800 mg, there is an initial redistribution phase of 6–10 hours followed by a plateau in serum levels for 24 hours or more. With these larger doses, there is no significant dose-dependent difference in serum concentrations within the first 48 hours (Figure 5).[19] During this period, serum RU 486 levels are in the micromolar range (i.e., 2.5 μmol/L). One of the possible explanations for this unusual pattern of metabolism is in fact that orosomucoid binding sites are saturated at doses of RU 486 above 100 mg.[19] Following oral administration, detectable levels of unmetabolized RU 486 have been found in the circulation for up to 10 days.[19] The major excretory pathway for RU 486 is fecal, with less than 10% being recovered in the urine.[15]

Animal studies have shown that the first steps of RU 486 metabolism involve a two-step demethylation of the (dimethylamino)phenyl ring at the C11 position and hydroxylation of the 17-propynyl chain (Figure 5). The demethylated metabolites are further hydroxylated or acetylated.[15] In the human, micromolar concentrations of monodemethylated, didemethylated, and the non-demethylated hydroxylated metabolite were ob-

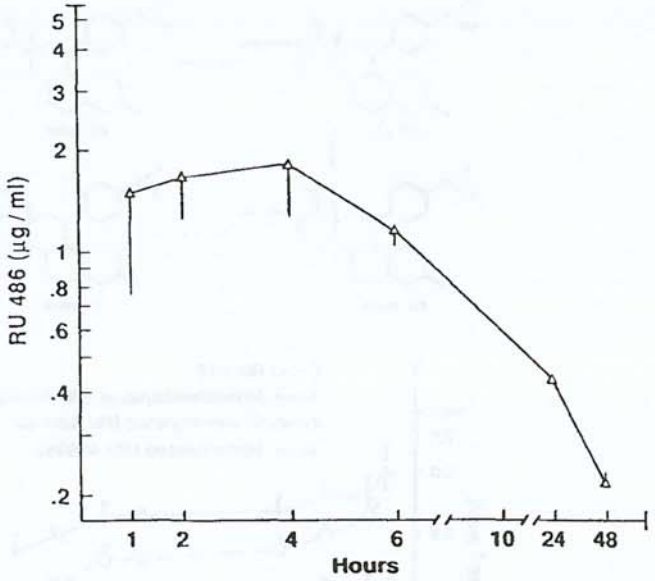

FIGURE 4. Half disappearance time of RU 486 following administration of 50 mg in the mid-luteal phase. Results show mean ± SEM in 5 subjects. Modified from Shoupe et al.[20]

served within 1 hour after oral administration of RU 486 (Figure 5). In contrast to the parent compound, circulating concentrations of metabolites increase in a dose-dependent fashion and with higher doses, the metabolite concentrations, especially the monodemethylated derivative, are in excess of the parent compound.[19]

The monodemethylated and hydroxylated derivatives interrupt pregnancy in the rat with a potency one-third that of RU 486. The antiglucocorticoid activity of these compounds are also one-third that of RU 486. The didemethylated compound, however, is clearly less potent than the other metabolites in the rat.[15] The biological effects of each of these metabolites have not been evaluated directly in humans; however, they do bind to the human progesterone and glucocorticoid receptors and even though the affinity is less than that of RU 486, these metabolites may contribute to the overall effects of the drug in view of their high concentrations in serum.[21]

Although RU 486 is distributed into all tissues of the rat,[15] the tissue distribution in humans is less well studied. In women, RU 486 and its demethylated metabolites were detected in the myometrium and abdominal adipose tissue collected during hysterectomy 12–15 hours after oral administration of 200 mg of the antiprogestin.[22] This dose resulted in

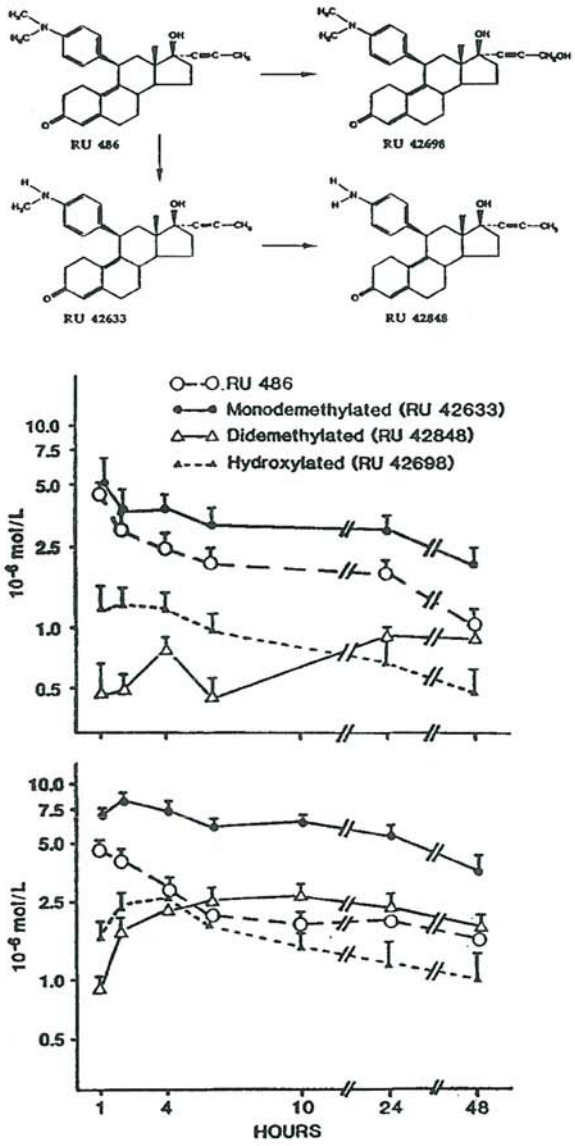

FIGURE 5. The upper panel depicts the metabolism of RU 486 into its monodemethylated (RU 42633), didemethylated (RU 42848), and alcoholic nondemethylated (RU 42698) derivatives. The mean (+ SEM) concentration of RU 486 and these three metabolites after oral administration of 100 mg and 600 mg in five subjects is shown in the middle and lower panels, respectively. Redrawn from Lähteenmäki et al.[19] The concentrations of RU 486 were similar after these doses, but the concentrations of metabolites were higher after 600 mg RU 486.

myometrial concentrations similar to those required to produce maximal stimulation of prostaglandin synthesis of human endometrial tissue in vitro.[23,24] As noted below, this action is believed to be one of the major reasons why this agent induces abortion. Lower than expected levels of RU 486 in fat are believed to be due to its avid binding to serum protein.[22] Studies have also shown that RU 486 and its monodemethylated metabolite cross the placental barrier during the second trimester.[25,26] In monkeys, it has been suggested that the efficacy of placental transfer may decrease with advancing pregnancy.[27]

V. Major Biological Effects

A. Antiglucocorticoid/Glucocorticoid Actions

RU 486 has been shown to have antiglucocorticoid activity by a broad array of in vivo and in vitro studies.[8,28] In view of its use as an antiprogestin in normal women, its antiglucocorticoid effects on the hypothalamic-pituitary-adrenal axis are of particular interest. RU 486 was found to have a dose-dependent inhibitory effect on the negative feedback of cortisol on ACTH secretion.[29-31] Single RU 486 doses of 1 and 2.2 mg/kg in women and men, respectively, were insufficient to produce this effect, but 4 mg/kg in women and 4.5 and 6 mg/kg in men led to a significant rise in ACTH and cortisol.[29] The inhibition of the morning rise of ACTH, β-endorphin, and cortisol levels by 1 mg dexamethsone administered at midnight was abolished by a single dose of RU 486 (6 mg/kg) administered at the same time.[29] In humans, it was estimated that the optimal antiglucocorticoid effect occurs when the RU 486:cortisol ratio in serum is approximately 10:1.[32]

The central antiglucocorticoid effect of RU 486 is particularly evident during the morning hours when cortisol levels are rapidly increasing. Thus, the midnight intake of RU 486 (6 mg/kg) by inhibiting the negative feedback of cortisol upon the hypothalamic pituitary axis enhanced the increase of serum ACTH, β-endorphin, and cortisol during the subsequent morning, i.e., 8–12 hours after drug ingestion. There were no changes in these parameters within 8–14 hours of ingestion of the same dose of RU 486 when it was given in the morning; however, on the following morning, the 8:00 a.m. values were again higher than in controls.[29] Thus, the effect of RU 486 on the pituitary-adrenal system occurs only at a specific time of day. Since this enhanced cortisol response presumably represents an attempt to compensate for possible peripheral glucocorticoid antagonism and resultant hypoadrenalism, it appeared logical to administer RU 486 in the evening to permit the subsequent increase in endogenous glucocorticoids the next morning to compensate for any possible antiglucocorticoid action. It is of note, however, that these findings were derived from studies using lower doses of RU 486 (6 mg/Kg) than the single 600 mg

(10 mg/Kg) dose currently used in women for abortion induction. The latter dose results in elevated cortisol levels throughout the day. Therefore, it remained important to determine whether the rise in serum cortisol levels was sufficient to compensate for peripheral receptor blockade. Accordingly, dogs were treated daily with 4-fold the usual human dose.[33] After 10 days of continuous treatment, no objective evidence of cortisol deficiency was observed. These conclusions were based on observations that signs of glucocorticoid deficiency developed over 2–10 days in untreated adrenalectomized dogs. Thus, the rise in serum cortisol can compensate for peripheral receptor blockade.

It should be pointed out that higher doses of RU 486 are required to produce an antiglucocorticoid as opposed to an antiprogestin effect.[20,29] For example, at the endometrium, bleeding ensues following RU 486 administration of 1 mg/kg[20] and changes in endometrial morphology occur with a dose as low as 0.1 mg/kg.[34] The fact that higher doses are required for antiglucocorticoid effects is probably related to the high concentrations of cortisol in blood, due to the inhibition of the feedback regulation of the pituitary-adrenal axis and to the fact that many glucocorticoid effects are permissive.[32] Nonetheless, the RU 486 dose customarily given to women to induce abortion (600 mg) routinely stimulates the hypothalamo-pituitary adrenal axis.

To date, no objective clinical or laboratory manifestations of overt glucocorticoid deficiency have been reported as a result of short-term administration of RU 486 as an antiprogestin in humans. Furthermore, the regulation of the pituitary-adrenal axis is not compromised following three months of treatment with RU 486 in doses of 100 mg/day.[35] Even though persistent elevations of ACTH and cortisol were observed, the acute stimulating effect of corticotropin releasing hormone remained unchanged and the diurnal rhythm was maintained.[35] This finding implies that the central regulatory control mechanisms remain intact during long-term treatment. There are no known consequences of the elevated ACTH and cortisol levels in subjects receiving low doses. In some subjects with breast carcinoma or inoperable meningioma receiving higher doses (200–400 mg/day) for many months, symptoms compatible with cortisol deficiency developed which appeared to reverse with dexamethasone.[36–38] The symptoms, which were worse at the onset of therapy, included weakness, nausea, and vomiting.[38,39] Other signs of cortisol deficiency found in adrenalectomized patients, such as fever, change in blood pressure, water intolerance, or persistent elevation of total eosinophils were not observed. When high doses of RU 486 (10 mg/kg/day) were administered to normal men for 14 days, one developed symptoms compatible with cortisol deficiency.[40] However, in this patient and in those reviewed above, there have not been objective signs of cortisol deficiency and, in fact, adverse reactions to the drug were a plausible alternative explanation for

the symptoms observed. Apparent adrenal insufficiency did, however, develop in two subjects with fixed cortisol secretion treated with doses of RU 486 ranging from 10–22 mg/kg/day for inoperable Cushing's syndrome.[32] Since measurement of serum cortisol cannot be used to establish the diagnosis of functional hypocortisolism during receptor blockade, clinicians will have to resort to seemingly antiquated in vivo end points that develop in the absence of glucocorticoids, such as eosinophilia and water intolerance, and focus on how such parameters change with glucocorticoid treatment of patients taking large dose of RU 486. For the time being, it is clear that most patients with an intact pituitary-adrenal axis compensate for glucocorticoid receptor blockade by elevating serum cortisol.

In addition to increasing ACTH and cortisol, long-term RU 486 treatment also increased the serum levels of the adrenal androgens androstenedione and DHEA.[36,37,39] Serum estradiol concentrations were also increased in subjects treated with 200–400 mg RU 486 daily.[36,37,39] As the estradiol levels were correlated with both androstenedione and cortisol levels,[37,39] it is highly likely that the increments in estradiol were due to aromatization of adrenal androgens in nonendocrine tissues.[36,37,39] It should be noted that not all studies have reported a rise in serum estradiol levels with RU 486. We failed to observe estradiol elevation following long-term administration of 200 mg daily to both men and women with inoperable meningioma (I.M. Spitz, manuscript in preparation), and Kettel et al.[35] reported no change in serum estradiol following administration of 100 mg daily for three months in patients with endometriosis.

There is also some evidence that RU 486 may act as a partial glucocorticoid agonist. Thus, it suppressed the ACTH response to ovine corticotropin releasing hormone in subjects with adrenal insufficiency, although to a far lesser degree than cortisol. On a weight basis, its relative glucocorticoid agonist activity was estimated to be approximately 1/250 that of cortisol.[41] Significantly, however, RU 486 was unable to support life in the adrenalectomized monkey.[42]

B. Antiprogestin Actions

1. Effects on the endometrium. Administration of RU 486 in single doses of 50–800 mg on days 6–8 of the luteal phase to normal women induced profound changes in endometrial histology consistent with progesterone withdrawal,[34,43,44] and menstrual bleeding invariably ensued within 72 hours.[20,45] When a single dose of RU 486 (200 mg) was given 2 days after the LH peak, a retardation of luteal phase development of the endometrium began as early as 12 hours after RU 486 intake.[43] In another study a single dose ranging from 5–200 mg given at various times during the

first half of the luteal phase inhibited endometrial glandular secretory activity, accelerated degenerative changes, induced various vascular changes, and increased stromal but not glandular mitotic activity.[34] Interestingly, a significant endometrial response of one or more of 17 morphologic features was observed at all doses studied, whereas induction of menstruation occurred only with the higher doses. This finding indicates that the antiprogestational action of RU 486 on endometrial morphology occurs at much lower doses than those that will induce endometrial bleeding.

In postmenopausal women receiving estrogen replacement, RU 486 unexpectedly produced agonistic effects on the endometrium, including induction of secretory changes, increased estradiol dehydrogenase, and reduced DNA polymerase activity—effects that were also produced when progesterone was administered to estrogen-treated women.[46] However, in estradiol plus progesterone-treated postmenopausal women, RU 486 antagonized the action of progesterone.[46] Similar findings were observed in ovariectomized monkeys.[47,48] That is, in estradiol plus progesterone-treated monkeys, RU 486 behaved as a classical progestin antagonist preventing the endometrial secretory transformation. By contrast, in estradiol-treated ovariectomized monkeys, low doses of RU 486 (1 mg/kg/day) acted as a progestin agonist and induced endometrial secretory transformation, whereas a higher dose (5 mg/kg/day) inhibited both endometrial proliferation and secretory activity. Thus, in the absence of progesterone, the high dose of RU 486 has anti-proliferative (anti-estrogenic) actions. This effect of RU 486 does not depend on the estrogen receptor since neither RU 486 nor its principal metabolites bind to this receptor.[8,48] Since high doses of progestins produce similar anti-mitogenic effects[49] and lead to endometrial atrophy, this action of RU 486 should be regarded as agonistic. In view of this anti-estrogenic action, one possible use for RU 486 could be in the control of estrogen-dependent tissue growth such as endometriosis and breast carcinoma. However, if this were the only action of RU 486 on endometrium and mammary epithelium, then its use for these diseases may not be practical in view of the lower cost of progestins and the fact that RU 486 may elevate estradiol in postmenopausal women by peripheral aromatization of adrenal androgens.[36,37,39]

In pregnant monkeys, RU 486 stimulated a rise of estradiol receptors in the decidua and myometrium.[50] These results were interpreted as showing an antagonistic action of RU 486 since progesterone decreases estrogen receptor synthesis.[49,51] Berthois et al.[44] reached a similar conclusion from observations in women treated with RU 486 (10 mg/day) for 4 days starting at the time of ovulation in that the concentrations of immunostainable estrogen and progesterone receptors were higher in endometrial glands and stroma from treated women compared to the control subjects, in which the receptor concentration showed the expected luteal phase de-

crease.[51] While this may be the correct interpretation of the action of this drug during pregnancy and the luteal period when progesterone levels are elevated, a study in ovariectomized, estradiol-treated monkeys showed that RU 486 produced a dose-dependent increase in endometrial receptors even in the absence of progesterone.[52] These latter findings were unexpected and suggest that RU 486 may directly stimulate a progesterone receptor-mediated rise in estrogen receptors independent of its ability to block the action of progesterone. Such observations suggest that some of the agonistic actions of RU 486 do not mimic the actions of progesterone.

The above observations on the actions of RU 486 on the uterus suggest that binding of RU 486 to the PR in the presence of progesterone results in a steroid-receptor complex that is transcriptionally inactive on many progesterone-responsive genes (Figure 3) (i.e., RU 486 is an antagonist of progesterone). However, in the absence of progesterone, RU 486 may form a receptor complex that is active on some promoters (i.e., the potential agonistic effects of RU 486). It is interesting that some of these latter effects may or may not mimic the effects of progesterone. It is the diverse agonistic effects of RU 486 that may give it some of its unique antineoplastic properties in breast cancer and meningioma as noted below.

The question arises as to whether the menstrual bleeding consequent to RU 486 administration results because of a direct action on the endometrium or whether this is an effect on the hypothalamic-pituitary-ovarian axis. This issue was addressed by administering human chorionic gonadotropin (hCG) during the luteal phase of the reproductive cycle in women to simulate early pregnancy by increasing estradiol and progesterone levels and delaying the onset of bleeding. This treatment did not prevent bleeding induced by an adequate dose of RU 486.[53-55] Thus, by maintaining corpus luteum function with exogenous hCG, RU 486 induced endometrial bleeding despite high circulating progesterone and estradiol levels.[53-55] This indicates that RU 486 acts directly at the level of the endometrium.

2. Effects on gonadotropin secretion. In a rat pituitary cell culture system primed with estradiol, RU 486 inhibited GnRH-induced LH and FSH secretion in a dose-dependent manner without affecting basal gonadotropin release. The inhibition was specific and antagonized by the addition of progesterone.[56] Progesterone itself stimulated GnRH-induced gonadotropin secretion.[56] A separate line of studies suggested that gonadotropin inhibition by RU 486 could operate at the hypothalamic level.[57] Preovulatory RU 486 administration blocked the LH surge in monkeys, an effect which could not be reversed by simultaneous treatment with dexamethasone.[58] These results suggest that the antigonadotropic effects of RU 486 are due to its antiprogestational rather than its antiglucocorticoid properties. Such observations also support the postulate that the small rise in progesterone in the late follicular phase facilitates the LH surge.

Many studies also indicate that RU 486 reduces gonadotropin secretion in humans. When 100 mg RU 486 was given from days 10–17 of the cycle, the LH surge was attenuated.[59] A single dose of 10 mg or 100 mg RU 486 produced an immediate reduction in LH and FSH concentrations when administered in the mid and late follicular phase. The decrease in mean LH concentration was consequent to a reduction in amplitude of the LH pulses released by the pituitary without any alteration in LH pulse frequency. The reduction in mean LH concentration was greater in those women with higher plasma estradiol concentrations.[60] Not all investigators have observed such dramatic changes during the follicular phase.[61,62] During the mid-luteal phase, RU 486 also decreased mean LH secretion and LH pulse amplitude and blunted the pituitary response to GnRH. In the late luteal phase, both LH pulse frequency and amplitude decreased.[53] In contrast to these short-term studies showing that RU 486 inhibits pituitary gonadotropin secretion, long-term treatment (50–100 mg/day for 3 months) increased mean LH and LH pulse amplitude without a change in FSH.[35,63] These elevated LH values may be transient and, after 4 weeks of treatment, levels are reported to return to baseline.[63] In view of the fact that RU 486 could act both on the hypothalamus as well as the pituitary and due to its antagonistic as well as agonistic actions, it is not surprising that its effects on LH and FSH secretion are diverse.

In addition to its activity on LH, FSH and ACTH, RU 486 also influences prolactin secretion. Healy et al.[64] observed that RU 486 suppressed basal hyperprolactinemia in ovariectomized Rhesus monkeys receiving steroid replacement. In normal women, however, a single dose of 50–800 mg RU 486 produced a transient dose-dependent increase in serum prolactin levels.[20] A similar rise has also been reported in a group of women receiving RU 486 for termination of pregnancy.[65] The precise mechanism for this increase in prolactin is not known.

3. Effects on the pregnant uterus. The antiprogestin action of RU 486 is targeted to the decidua, which contains a high concentration of progesterone receptors. Receptor blockade results in withdrawal of progesterone support to the endometrium, menstrual bleeding, and disruption of placental function. At this time, circulating levels of estradiol and progesterone are high. Bleeding also invariably occurs in those subjects who fail to respond to RU 486 with complete abortion. In those women who do abort, the decline in hCG appears to be a secondary phenomenon consequent to detachment of chorionic tissue of the blastocyst from the uterine wall. The fall in hCG, in turn, leads to luteolysis and a further withdrawal of hormonal support of the endometrium. Thus, the direct action of this drug on uterine cells triggers a series of events that leads to the expulsion of the placenta and the return of cyclic ovarian function. In vitro studies showed that RU 486 may act directly on the syncytiotro-

phoblast and produce a dose-dependent decrease in β-hCG, human placental lactogen, and progesterone secretion.[66] Whether this plays a role in abortion induction remains to be established.

An increase in prostaglandin (PG) action is also crucial in the induction of the abortive process. Csapo[67] proposed that the spontaneous level of uterine activity is regulated by the balance between an intrinsic suppressor progesterone and the stimulator $PGF_{2\alpha}$. During pregnancy, uterine activity is suppressed. Among physiological events associated with spontaneous abortion and labor is an increase of endogenous $PGF_{2\alpha}$ production. RU 486 and ZK 98734 stimulated the in vitro release of $PGF_{2\alpha}$ from decidual glandular cells and endometrial stromal cells.[23,24] Furthermore, treatment of women with RU 486 for 36 hours prior to surgical termination of pregnancy resulted in an increased production of $PGF_{2\alpha}$ in decidual cultures prepared from the abortuses. A significant decrease in a metabolite of $PGF_{2\alpha}$ in these cultures was also observed 24 hours after pretreatment of pregnant women with RU 486.[68] These results suggested that the increased uterine activity observed after RU 486 is probably due to stimulation of endogenous prostaglandin production and inhibition of prostaglandin metabolism.[23,24,68] Recently, it has been shown that there is a marked reduction in the concentration of prostaglandin dehydrogenase, a key enzyme involved in the control of prostaglandin catabolism, in decidual tissue following RU 486. This enzyme is under progesterone control. These observations of a reduction in activity of prostaglandin dehydrogenase following RU 486 supports the idea that the major action of antiprogestin is on prostaglandin metabolism.[69] These observations also supported the findings of Norman et al.[70] who demonstrated that the increase in uterine contractility following RU 486 administration was maintained in women despite the administration of indomethacin, which inhibited in vitro the decidual synthesis of $PGF_{2\alpha}$.

Using a pressure transducer in the cervical canal, Bygdeman and Swahn[71] showed that RU 486 treatment resulted in regular uterine activity in contrast to the low level contractility found in untreated control patients. This response was related to the withdrawal of progesterone support. In the uterus unprimed with RU 486, prostaglandins induced an increase in uterine tone; however, after priming with RU 486, this increase in tone was accompanied by coordinated contractions with increase in amplitude and frequency. Thus, RU 486 increases the sensitivity of the myometrium to prostaglandins.[71]

4. Effects on the cervix. Marked softening and dilation of the cervix, which is termed cervical priming, was reported at the time of uterine evacuation in women treated with RU 486 who had an incomplete abortion. This was confirmed in studies that objectively assessed the ability of RU 486 to dilate the cervix in subjects undergoing late first trimester

surgically-induced abortion.[72–74] This was initially postulated to be a consequence of increased local prostaglandin release. However, no differences in prostaglandin synthesis were observed in cervical biopsies taken from women undergoing surgical abortion with or without RU 486 pretreatment.[72] Since mechanical dilation of the cervix is traumatic during the first trimester of pregnancy, this is a highly beneficial effect of RU 486 even if the abortion is not complete since subsequent vacuum aspiration is much easier.

5. Effects on the ovary. Several *in vitro* studies suggested that RU 486 can also act directly on ovarian cells. An early study showed that RU 486 4–40 ng/ml) suppressed progesterone production from cultured human granulosa cells.[75] In view of the high concentrations of RU 486 (100 μg/ml) required to inhibit the LH-induced stimulation of progesterone from cultured human granulosa cells, this effect of RU 486 probably represents a direct effect upon enzymes involved in synthesis rather than a receptor-mediated response.[76]

In humans, follicular phase RU 486 administration may delay the emergence of the preovulatory progesterone rise which is most likely due to an effect on gonadotropin secretion.[59,77] Likewise, the suppression of estradiol noted during follicular phase RU 486 administration is also probably secondary to inhibition of gonadotropins.[59] Indeed, in monkeys,[16] RU 486 administered daily in the early follicular phase blocked ovulation unless an ovulatory induction regimen of hMG/hCG was given. These findings lend support to the fact that RU 486 inhibits pituitary gonadotropin secretion. Furthermore, if there is a significant effect on ovarian steroidogenesis in vivo, it can be overcome by gonadotropins.

VI. Clinical Utility

A. Abortion Induction

1. Clinical results. In 1982, Herrmann et al.[78] were the first to use RU 486 in humans for successful termination of pregnancy in 9 out of 11 subjects with amenorrhea of 6–8 weeks' duration. Since then, different regimens have been utilized with total dosages ranging from 140 to 1600 mg administered over one to seven days to women with amenorrhea of up to 9 weeks in duration.[30,31,79–81]

When RU 486 is used alone, the success rate in women with amenorrhea of less than 7 weeks usually varied from 64–85%,[31,78–80] although in some series this was somewhat lower.[30,31] Side effects reported included nausea, vomiting, and uterine cramps. Although it was not easy to dissociate these symptoms from those occurring in normal pregnancy and abortion induced by other procedures, nausea and vomiting are noted by men who receive this agent.[38,39] RU 486 failed to induce bleeding in 1–10% of

subjects and resulted in incomplete expulsions in 10–30%.[2] The most reliable index predicting a favorable outcome following RU 486 was a fall in serum β-hCG within one week of the onset of therapy. Non-responders failed to demonstrate this decline.[80]

2. Reasons for non-responsiveness. In all monkeys treated with an effective dose of RU 486, shedding of the endometrium appears to be uniform in different parts of the uterus.[82] This, however, does not occur in all humans.[83] If menstrual induction is not associated with complete shedding of the functional layer of the endometrium, it is possible for a pregnancy to continue. These observations provide one of several lines of evidence considered in this review suggesting important species differences in the action of RU 486. Thus, studies in non-human primates are unlikely to give insight into the reasons for failure of RU 486 in humans.

There is probably no single reason why a significant percentage of women do not respond to RU 486, but there are several possibilities: the first and most obvious is failure to administer the drug early in pregnancy. The success of RU 486-induced abortion is lower in women with more advanced pregnancies.[81] In several series, it was observed that women with higher initial levels of β-hCG and progesterone, which are indicators of more advanced pregnancies, do not respond as well as those with lower levels.[31,79,84] A second reason for lack of response is failure to administer an adequate dose of RU 486. A few studies suggest that non-responsiveness does not appear to be related to the dose of RU 486 administered. Thus, Birgerson and Odlind[79] administered 20, 50, or 100 mg RU 486 daily for 7 days to 153 women and observed no significant difference in efficacy between the three dose regimens, the percent of subjects with complete abortion varying from 64–73%. The fact that such studies may not have had the ability to distinguish the difference in doses was suggested by the observations that the success rate was lower in subjects with a larger body mass.[84] Third, as noted above (Figure 2), genetic variations of the progesterone receptor such as a mutation of Gly^{722} could also result in selective loss of RU 486 binding.[12] Fourth, studies in dogs suggested that variability in the actions of RU 486 was related to variations in drug metabolism;[85] however, differences in the pharmacokinetics of RU 486 and its metabolites have yet to be detected in those who fail to respond to this agent.[86] Fifth, increased orosomucoid levels could also account for non-responsiveness by decreasing the availability of unbound RU 486.[18] However, no differences in this protein were detected between responders and non-responders.[86] Finally, the most important factor accounting for the non-responsiveness is believed to be an inadequate RU 486-induced increase in endogenous accumulation of $PGF_{2\alpha}$ or in the response of the uterus to prostaglandin which, in turn, results in insufficient uterine contractility.[68–71]

3. Combination of RU 486 with prostaglandins. Bygdeman and Swahn[71] were the first to show the advantage of combining RU 486 with prostaglandins for pregnancy termination. RU 486 (50 to 100 mg/day) was administered for 4 days and an i.m. injection (0.25 mg) of the PGE analog 16-phenoxy-tetranor-PGE_2 methylsulfonylamide (sulprostone) was given on the fourth day of RU 486 administration. This combined treatment resulted in complete abortion in 32 of 34 subjects, a rate that was higher than when RU 486 was used alone. These results have been duplicated in numerous other studies using intramuscular, vaginal, or oral prostaglandin preparations following RU 486 pretreatment. In a comprehensive French experience from 73 centers, 2,115 women with amenorrhea of 49 days or less were given 600 mg RU 486 followed in 36–48 hours by the vaginal pessary gemeprost (16,16-dimethyl-trans-Δ_2 PGE_1 methyl ester; 1 mg) or i.m. sulprostone (0.25, 0.375 or 0.5 mg). The overall efficacy exceeded 96%.[87] Failures included persistent pregnancies and incomplete expulsion. Vacuum aspiration or dilation and curettage was performed in 0.9% of the women because of excessive uterine bleeding. Only one subject required blood transfusion. Expulsion usually occurred within 24 hours after prostaglandin administration, often within 4 hours, especially when a higher dose of the prostaglandin was given. The average duration of bleeding was 8.9 days and was significantly longer in women receiving the higher dose of prostaglandin. Most women reported abdominal pain during the first 4 hours after prostaglandin administration and this was more pronounced with the higher doses. Other side effects reported within these 4 hours included nausea (33.8%), vomiting (15.3%), and diarrhea (7.5%). These symptoms generally did not necessitate any treatment. Since this report, these workers have published results from 300 centers in which 16,173 subjects received a similar protocol.[88] The results of this large clinical trial supported the earlier conclusions.[87]

In a multicenter British trial comprising 588 women with amenorrhea up to 9 weeks, 600 mg RU 486 was given, followed 48 hours later by 1 mg gemeprost.[89] The overall complete incidence of abortion was 94%. Five women required both curettage and blood transfusion. In the 521 women in this study who had hemoglobin measured before and 7 days after treatment, there was little or no change in 93% of subjects and a decrease between 2.1–4.0 g/dl in 1.1%. Narcotic analgesia was required after gemeprost in 37% of nullipara and 13% multipara. Overall, 26% of the subjects had vomiting and 13% diarrhea.

When prostaglandins are used alone for abortion induction, the dosage requirements are much higher and a large percentage of subjects experience severe abdominal cramps, nausea, vomiting, and diarrhea.[90,91] Indeed, one small study comprising 97 women with amenorrhea of up to 8 weeks has been conducted to compare the effect of vacuum extraction with RU 486 and gemeprost.[90] For the non-surgical approach, RU 486 and gemeprost

were given either alone or in combination.[90] The dose of the vaginal suppository when used in combination with RU 486 was 1 mg. When used by itself, women received gemeprost 1 mg every 3 hours for up to 5 suppositories. The dose of RU 486 was not varied (150 mg daily for 4 days). The results showed that the incidence of complete abortion with vacuum extraction, gemeprost alone, and with the RU 486-gemeprost combination was similar. In contrast, the success rate for RU 486 administered alone was much lower. Side effects and analgesic requirements were much higher in women receiving gemeprost alone than in those receiving the combination. Despite the occurrence of side effects, 88% of subjects in one series responded affirmatively when asked whether they would elect to use the RU 486/gemeprost combination again if needed.[92]

Since greater pain and bleeding occur with larger doses of prostaglandins, lower doses have also been used. Rodger et al.[93] administered 600 mg RU 486, followed 48 hours later by either 0.5 or 1 mg gemeprost. There was no difference in the effectiveness, but the incidence of severe pain was less with the smaller dose. In another study, an attempt was made to relate the amount of blood loss to drug dose. Abortion was induced in 222 women with amenorrhea of less than 63 days using RU 486 (600 mg) and 0.5 or 1 mg gemeprost.[94] Although there was wide individual variation, the total median measured blood loss was 74 ml. This was similar to that reported for RU 486 alone, vaginal gemeprost alone, or vacuum aspiration.[94] It should be noted that the amount of blood loss was independent of the dose of RU 486 or gemeprost, but increased with an increase in gestational age.[93]

Roussel Uclaf has now accumulated experience with over 120,000 subjects in France who have received RU 486 together with prostaglandin. Large clinical trials have also been conducted in over 20 countries and have confirmed the initial experience (Ulmann, personal communication). Unlike treatment with RU 486 alone where the success rate decreased with advancing amenorrhea after 7 weeks,[81] the combination was effective up to 9 weeks of gestation;[89] in published studies, the incidence of abortion induction ranged from 92.7% to 99%.

In the large study by Ulmann et al.,[88] significant cardiovascular side effects were reported in 4 cases. In 3 subjects, there was severe hypotension necessitating infusion of macromolecular solutes. There was also one acute myocardial infarction in a 38-year-old smoker. In these 4 subjects, symptoms commenced within 1 hour of sulprostone administration and all recovered uneventfully. However, in another study, there was a fatal myocardial infarction following sulprostone in a 31-year-old heavy smoker.[91] As a consequence, parenteral prostaglandins should be used cautiously in women with heart disease and, although not absolutely contraindicated, it is not recommended in women over age 35 or who are heavy smokers. Because of the inconvenience of sulprostone and geme-

prost, which require refrigeration, and the cardiovascular side effects seen with sulprostone, alternate prostaglandin preparations are now being evaluated. Cytotec or misoprostol (methyl 11α, 16-dihydroxy-16-methyl-9-oxoprost-13 E-en-1-oate) is a stable prostaglandin E_1 analog that has been safely used for the treatment of gastric ulcers for many years; for this indication, it is given in an oral dose of 200 μg four times daily. Its effects on uterine tone are similar to those of other prostaglandins.[95] In a recent published study in women with amenorrhea of under 50 days, one group, comprising 505 women, received 400 μg misoprostol 48 hours after RU 486; the success rate for termination of pregnancy was 96.9%. A second group of 390 women initially followed the same protocol, but if pregnancy was not terminated within four hours after misoprostol, the women were offered an additional 200 μg dose. In this second group, the overall success rate was 98.7%. These results indicate that the combination of RU 486 and misoprostol is as effective as RU 486 and parenteral or vaginal prostaglandin administration for the termination of early pregnancy in subjects with amenorrhea of under 50 days. Side effects were neither more frequent nor more severe than after parenteral or vaginal prostaglandin preparations.[96] Thong and Baird[97] noted complete abortion in 92 out of 99 women with amenorrhea of less than 50 days who were given 200 mg RU 486, followed 48 hours later by 600 μg misoprostol. There were three on-going pregnancies and four incomplete abortions. A total of 24% of women vomited and 7% had diarrhea. No analgesia was needed in 62% of the women. Expanded trials are warranted to determine whether misoprostol has less side effects than other prostaglandins that have been used with RU 486. These studies should be facilitated by the recent approval by the French government of the use of misoprostol with RU 486.

B. Inhibition of Ovulation

When RU 486 3 mg/kg) was administered for 3 consecutive days after ultrasonic demonstration of a dominant follicle, there was collapse of this follicle, prolongation of the follicular phase, postponement of the LH surge, and a delay in ovulation.[62] Other workers have also noted that mid and late follicular phase RU 486 administration interrupts normal follicular development and delays ovulation.[45,59,98] Following cessation of RU 486, there is resumption of follicular growth or reinitiation of new follicular recruitment with eventual ovulation.[45,59]

In view of its ability to arrest follicular development and delay the LH surge, attempts have been made to use RU 486 as a contraceptive agent to block ovulation. To be successful, RU 486 must be administered either continuously or at regular intervals to prevent the emergence of a dominant follicle. Continuous administration of RU 486 in a dose of 2 mg, 5 mg, or 10 mg daily for one month resulted in inhibition of ovulation with

a delay in menstruation.[99,100] There also appeared to be evidence of luteal deficiency in the recovery cycle.[99] Since 1 mg RU 486 daily did not consistently inhibit ovulation, it appears that 2 mg is the threshold dose.[77,100]

Continuous RU 486 treatment resulted in unopposed, albeit low, serum estradiol concentrations. This potential stimulatory effect on the endometrium could be obviated by adding a progestin following RU 486 to produce regular withdrawal bleeding. To this end, Kekkonen et al.[101] administered RU 486 (25 mg) from days 1–14 followed by norethisterone from days 15–24 to promote suppression of follicular growth and secretory transformation of the endometrium, respectively. Women were treated for up to 3 consecutive cycles. This regimen promoted well-controlled bleeding, but ovulation was not consistently blocked. Other RU 486-progestin combinations have been attempted with similar results (Lähteenmäki and Croxatto, unpublished).

Intermittent RU 486 administration was also tested. Oral administration of 25 mg once weekly to monkeys inhibited ovulation as evidenced by blockade of the expected midcycle LH and FSH surge and by the fact that progesterone levels remained undetectable.[102] Inhibition of progesterone secretion was not complete when half the dose of RU 486 was administered.[102] When this regimen was applied to women, unlike the monkey, suppression of progesterone was not consistently observed in subjects receiving 10 or 50 mg once weekly for 5 weeks or 50 mg for 3 successive days at 10-day intervals for 3 months. RU 486 measurements in serum indicated that the inability to inhibit ovulation with this approach was not due to failure to take the drug.[103] Thus, present studies suggest that with the doses and regimens tested to date, RU 486 administration does not uniformly inhibit ovulation.

As noted above, the endometrium appears to be more sensitive to RU 486 than the pituitary.[34] The observation that a single dose of RU 486 (10 mg) administered 5 and 8 days after the LH surge disrupted endometrial regulation without disturbing the hormonal events of the cycle supports this postulate.[104] These observations suggested an alternate approach to contraception.[43] Swahn et al.[43] administered a single 200 mg dose of RU 486 on the second day after the LH peak. This resulted in endometrial retardation that was evident 12 hours after RU 486 and became more prominent after 36 and 84 hours. This regimen did not alter the length of the cycle or serum FSH, E_2, and P levels. When this strategy was applied to 18 unprotected women for a total of 80 cycles, only one clinical pregnancy resulted.[105] However, for this approach to receive wide application, a simple method of detecting the LH surge is required. Further studies need to be conducted to determine if RU 486 has any contraceptive potential by rendering the endometrium inimical to implantation; however, at this stage, RU 486 cannot be recommended as a contraceptive agent that blocks cyclic ovarian activity.

C. Menses Induction

A contraceptive that could be administered either one or several days each month to induce menses whether or not pregnancy has occurred would be an attractive form of birth control for many women. In view of its mechanism of action, it seemed that antiprogestins would be candidates for such a method and studies in monkeys showed promising results.[54]

Administration of RU 486 (3 mg/kg) to 10 women for 3 days in the mid luteal phase induced uniform uterine bleeding within 36–72 hours after the onset of treatment;[53] in 8 of these women, luteolysis did not occur. This was evidenced by an initial decline of serum estradiol without a change in progesterone levels, a rebound increase in LH, estradiol and progesterone in 3 days, and the onset of the second episode of uterine bleeding when spontaneous luteolysis ensued. These findings were confirmed by other authors.[45,54,59] For this reason, RU 486 was administered in the late luteal phase near the time of expected menses.

As anticipated, when the drug was given in the late luteal phase, only one bleeding episode was observed. This usually commenced within 24–48 hours after RU 486 administration.[53,106] Such treatment often shortened the luteal phase with prolongation of the follicular phase of the untreated cycle that followed. Luteolysis was even further accelerated in the late luteal phase when GnRH antagonists were administered together with RU 486.[107] In another study, RU 486 (100 mg) was given for 4 consecutive days prior to the expected menses in three successive cycles to women who were not sexually active.[106] This was preceded and followed by two placebo-treatment cycles. Bleeding patterns were similar between RU 486-treated and placebo cycles. Daily measurement of urinary estrone glucuronide and pregnanediol glucuronide suggested that ovulation had occurred and was followed by appropriate corpus luteum function during treatment and post-treatment cycles (Figure 6). It was concluded that RU 486 had no major effect on menstrual cycle events if it was administered at the time of expected menses, when progesterone withdrawal would normally occur.

Since late luteal phase RU 486 administration did not disturb the events of the menstrual cycle, studies were undertaken in unprotected women to determine if RU 486 could serve as a menses regulator. A total of 5 studies were conducted.[108–112] All investigators gave RU 486 at the end of the luteal phase usually as a single 600 mg dose. However, one group[109] administered either 400 mg on a single occasion or 100 mg daily for six successive days. In another study,[111] the dose administered was either 400 or 600 mg. β-hCG levels were determined to document the number of subjects who conceived. In the majority of subjects, RU 486 did terminate pregnancy. However, the precise success rate was influenced by the

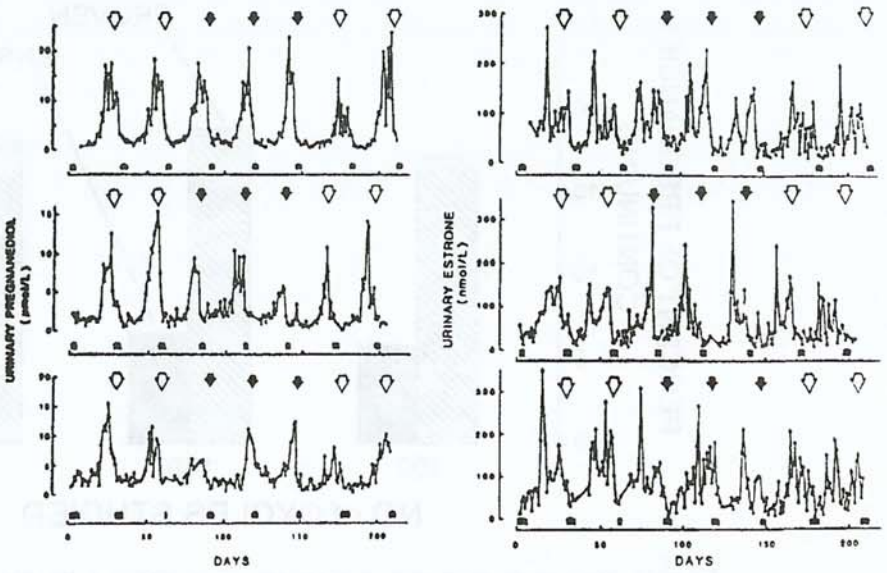

FIGURE 6. Urinary pregnanediol glucuconide (left panel) and estrone glucuronide (right panel) in 3 subjects during 2 pretreatment, 3 treatment, and 2 post-treatment cycles. Bleeding episodes are indicated by black bars. Filled arrows represent RU 486 treatment and open arrows the placebo. The dose of RU 486 administered was 100 mg daily for 4 days.

method of analysis. In the three largest studies, there were 35, 46 and 22 proven pregnancies in 102, 139 and 137 treated cycles, respectively.[110-112] Following RU 486 treatment, the percentage of continuing pregnancies as a function of the total number of cycles studied ranged from 2.9 to 8.3% (Figure 7). However, this is not a true reflection, since there was no conception in the majority of these cycles. Thus, when the failures are expressed in relation to the number of cycles with proven pregnancies, the rates ranged from 17.1 to 18.8% (Figure 7). These are similar to the failure rates expected when RU 486 is used without prostaglandins to terminate pregnancy in women with amenorrhea of less than 7 weeks' duration. This implies that responsiveness or nonresponsiveness to RU 486 is determined at a very early stage of gestation.

On occasion, when used as a monthly menses inducer, RU 486 prolonged the treatment cycle causing disruption of the menstrual rhythm.[108,112] For example, Couzinet et al.[112] had intended to examine 18 consecutive cycles in 12 subjects for a total of 216 cycles; however, only 137 cycles were completed since compliance was poor and there was general dissatisfaction with the method. Another disadvantage is that RU 486 did not induce bleeding in anovulatory cycles.[112]

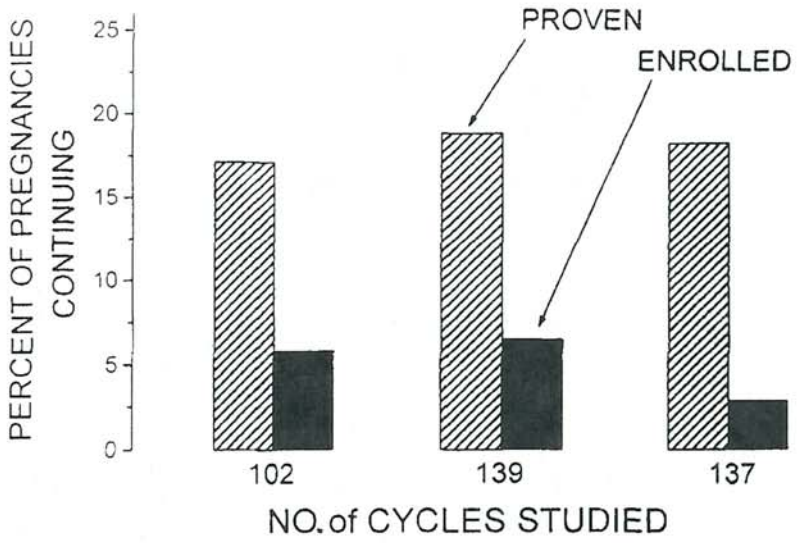

FIGURE 7. The percentage of continuing pregnancies in relation to the number of subjects enrolled and the number of subjects proven to be pregnant by detection of β-hCG in three studies.[110-112] The total number of cycles evaluated in each of these 3 studies is shown under each pair of bars.

D. Postcoital Contraception

RU 486 has also been used as a postcoital agent within 72 hours of unprotected intercourse.[113,114] In one recent randomized study,[114] a total of 402 women were given a single dose of 600 mg RU 486 and 398 received the standard regimen of 100 μg ethynylestradiol and 1 mg norgestrel administered on two occasions 12 hours apart. Although there were 4 pregnancies in the women receiving the standard regimen and none in those subjects given RU 486, the results were not significantly different. Webb[113] compared RU 486 (600 mg) to danazol as well as to the estrogen-progesterone regimen in a small preliminary study comprising a total of 215 subjects distributed among the three groups. There was one instance of proven pregnancy in the RU 486 group and this pregnancy was subsequently terminated with antiprogestin treatment. It is thus apparent that when used as a post-coital agent, the failure rate is low and appears to be equivalent or better than other postcoital contraceptive methods. Side effects were less with RU 486 than with the usual high-dose estrogen or estrogen plus progestin postcoital methods.[113] In addition, RU 486 may be effective for a longer time period after intercourse than steroid treatment that can be used only up to 72 hours.[108-110,113] It should be noted that in the study of Glasier et al.,[114] more women given RU 486 had a

delay in their menstrual bleeding than those receiving the standard therapy. Further studies are required to critically analyze the role of RU 486 as a postcoital agent.

E. Cervical Dilation

In view of the marked effect of RU 486 on the dilation of the cervix and on myometrial contractility, this agent was found to be useful in the preoperative preparations of women for first trimester vacuum aspiration. It is usually administered 30–48 hours prior to surgical abortion in a dose of 600 mg and is as effective as prostaglandins with significantly fewer side effects.[73,74,115]

In second trimester abortions, pretreatment with RU 486 reduced the interval between prostaglandin administration and expulsion. Furthermore, the dose of prostaglandin required was significantly reduced and women treated with RU 486 experienced considerably less pain than women who received placebo.[116] It is interesting that the effect on the cervix is maintained at a time when the endometrium has lost its responsiveness to RU 486. In view of these promising results, treatment with RU 486 followed by prostaglandin has been approved recently in France for the therapeutic termination of first and second trimester pregnancies.

Pretreatment with RU 486 also reduces the force required to dilate and soften the cervix particularly in non-pregnant, primigravid women.[74] This agent could, therefore, prove useful for planned outpatient procedures such as insertion or removal of an IUD, hysteroscopy, dilation and curettage, or other transcervical procedures requiring access to the uterine lumen. Because of its profound effects on endometrial histology, RU 486 should not be used prior to endometrial biopsy.

RU 486 has also been used for induction of labor following intrauterine fetal death. In one study, 600 mg was administered daily for 2 days and was considered effective in 29 of 46 subjects with only 8 successes in 48 placebo-treated controls.[117] This large double-blind study provided evidence that RU 486 has an application in the management of intrauterine fetal death. Indeed, RU 486 has been approved in France for induction of labor following fetal death. These results suggest that fetal death restores the sensitivity of the uterus to RU 486. Similarly, RU 486 has also been used for the expulsion of uterine contents following fetal death which may occur with various assisted reproductive techniques used in infertility.[118] Another proposed use of RU 486 is to induce labor at the end of the third trimester, although experiments in monkeys have not given uniform success. In one study in monkeys, RU 486 promoted uterine activity, but cervices showed little dilation and cesarean section was required.[119] In a further study in monkeys, RU 486 did induce cervical ripening but there were insufficient uterine contractions to induce labor unless oxytocin

was added.[120] By contrast, in a randomized double-blind study in women at term, Frydman and co-workers[121] administered either 200 mg RU 486 or placebo daily for 2 days. In the RU 486 group, 50% of the women underwent spontaneous labor compared with 25% in the placebo group. The mean time from onset of treatment and the start of labor was shorter in the RU 486 group. These results represent another example of a difference in response of humans and monkeys to RU 486. Alternatively, RU 486 may have been administered too early in the monkey.

The use of RU 486 at term prompted concern about its effect on the infant, since this agent crosses the feto-placental barrier.[25–27] One small study did show a rise in fetal aldosterone but no change in cortisol 4 hours after administration of 600 mg RU 486 for midterm pregnancy interruption.[26] Despite the fact that no untoward effects have been observed in the subjects or newborns to date, further studies are needed to establish the safety of RU 486 for induction of parturition near term before its use in pregnancies with normal infants can be routinely recommended.

F. Other Gynecological Indications

Both estrogen and progesterone receptors are present in ectopic endometrial tissue. It thus seemed reasonable to explore the properties of RU 486 for treatment of endometriosis. Kettel and co-workers[35] administered RU 486 100 mg/day for 3 months to 6 normally cycling women with endometriosis. There was an improvement in pelvic pain in all subjects even though there was no change in the extent of the disease as determined by follow-up laparoscopy. Although all women became anovulatory and amenorrheic during treatment, ovarian suppression was incomplete as evidenced by mid-follicular phase levels of urinary estrone glucuronide and serum estradiol.[35] Murphy et al.[63] administered RU 486 (50 mg) daily for 3 months to 10 patients with uterine leiomyomata. Compared to pretreatment values, leiomyomata volumes decreased 49% after 12 weeks of treatment. Further clinical trials need be conducted.

G. Treatment of Tumors

1. Breast carcinoma. In view of the unusual agonistic and antagonistic activity of RU 486 on the endometrium, it was important to explore the effect of this agent on breast tumors that have progesterone receptors. The response was tested on the growth of several human breast cancer lines in culture. A dose-dependent antiproliferative effect of RU 486 was observed that mimicked the action of progestins and this effect correlated with the progesterone receptor content. By contrast, RU 486 did not mimic the action of progestins on stimulating synthesis of two specific proteins and on accumulation of insulin receptors; however, when added together with progestins, RU 486 inhibited these progestin-specific effects.[122,123]

These studies on breast cancer cell lines confirmed the antiproliferative effect of RU 486 and emphasized again that this agent has both agonistic and antagonistic actions depending on the biological response measured. In view of the multiple and varied effects of RU 486 on tumor cells in vitro, the action of this agent should be explored on breast cancer and other tumors in vivo.

In rats, combined treatment with RU 486 and antiestrogens or LHRH agonists produced high remission rates of breast cancer.[36] In women, only results of preliminary clinical studies have been reported. In one pilot trial involving 22 postmenopausal or oophorectomized women with chemotherapy-resistant metastatic breast cancer, 4 individuals showed measurable tumor regression at 3 months of treatment with 200 mg RU 486.[124] In a further study in 11 postmenopausal women with metastatic breast carcinoma, RU 486 was administered in a daily dose of 200-400 mg for 3–34 weeks. There was one objective response, 6 instances of short-term stable disease, and in 4 there was progression.[36,37] To establish whether antiprogestins might form a treatment modality for the endocrine treatment of human breast cancer, long-term comparative studies will be required.

2. Meningioma. Most meningiomas are devoid of estrogen receptors but contain significant concentrations of progesterone receptors as visualized with immunostaining procedures.[125] RU 486 produced growth inhibition of meningioma cells in culture[126] and reduction in size of a human meningioma implanted into nude mice.[127] These studies supported the use of RU 486 for treatment of meningioma in humans. In one trial,[38] 200 mg RU 486 was given for periods from 2–31 months to a total of 14 patients with unresectable meningioma. Five patients showed signs of an objective response as measured by reduced tumor size on CT or MRI scanning or improved visual field examination. In addition, three experienced subjective improvement. These results argue that further control trials are indicated to document the extent to which RU 486 is efficacious for the treatment of this tumor. The fact that some treated subjects showed objective response when serum progesterone levels were low (i.e., men and postmenopausal women) argues that the agonistic actions of RU 486 were responsible for the antitumor effects.

3. Colon carcinoma. Some primary colonic carcinomas have been reported to have steroid hormone receptors for estrogen, progesterone, and glucocorticoids. Thus, RU 486 might have a potential role in treatment of this neoplasm.[128]

H. Antiglucocorticoid Applications

Nieman et al.[129] were the first to utilize the antiglucocorticoid properties of RU 486 to treat a patient with Cushing's syndrome due to ectopic ACTH

secretion. This group has treated 11 patients with Cushing's syndrome due to occult or unresectable ectopic ACTH-secreting tumors or inoperable adrenocortical cortisol-secreting carcinomas with doses of RU 486 from 5–22 mg/kg per day for periods ranging from 4 weeks to 1 year. In these patients with fixed cortisol secretion, it was possible to normalize the Cushinoid phenotype, ameliorate depression, decrease hypertension, eliminate carbohydrate intolerance, and correct glucocorticoid-induced gonadal and thyroid hormone suppression in 7 subjects.[32] This drug could, therefore, play a role in the preoperative preparation of a patient with Cushing's syndrome for surgery. By contrast, in Cushing's disease where cortisol secretion is not fixed, RU 486 cannot be recommended for routine treatment since the antiglucocorticoid will further enhance ACTH and cortisol secretion as central receptor blockade is established. These examples of the differential responses of Cushing's syndrome and Cushing's disease to RU 486, emphasize that the use of this agent as an antiglucocorticoid is not as straightforward as its use as an antiprogestin.

In general, the applications of RU 486 as an antiglucocorticoid may be thought of as local or systemic. Studies in rabbits provided a rationale for local application of eye drops containing RU 486 to lower intraocular pressure in humans with glaucoma.[130] It is unlikely that enough RU 486 could be administered by this route to increase adrenal cortisol secretion and overcome the receptor blockade. Systemic administration of an antiglucocorticoid could be used for the antagonism of large doses of exogenous glucocorticoid, as well as for inhibition of the physiological effects of endogenous cortisol. For systemic administration to be effective, however, the antagonist would need to have highly selective actions on specific organs. For example, RU 486 blocked the loss of muscle and body weight induced by pharmacologic doses of dexamethasone.[131] In this instance, if RU 486 is to have a potential use in the treatment of steroid-induced myopathy, it must have a selective antagonistic effect on muscle without attenuating the beneficial effects for which the glucocorticoid was given. A similar argument would apply to the treatment of the other undesired effects of high dose glucocorticoid therapy. Although there are many studies showing that RU 486 can antagonize the action of glucocorticoids, there are few that have emphasized the need for selective antagonism. It should be remembered that chemists have attempted without success to synthesize glucocorticoids with selective beneficial actions. Hopefully, these antagonists will have selective actions that will inhibit the catabolic, but not the anti-inflammatory, effects of glucocorticoids.

Systemic administration of RU 486 for neutralization of endogenous cortisol also could be of benefit in a wide variety of disorders. For example, muscle atrophy associated with conditions as diverse as androgen withdrawal, denervation, and muscular dystrophy is associated with increased glucocorticoid receptors in muscle, thus suggesting that endogenous corti-

sol is a regulator of muscle mass. This postulate was confirmed with the demonstration that RU 486 could attenuate muscle loss following orchidectomy.[132] Similarly, several studies showed that diseases caused by herpes and Maloney viruses in animals were prevented or inhibited by reducing glucocorticoid synthesis and that cortisol enhanced human immunodeficiency virus and cytomegalovirus expression. These observations suggested that antagonism of the action of endogenous cortisol could prevent progression of several serious viral diseases.[133] However, unless the specific action of cortisol that one wished to inhibit was sensitive to very low doses of RU 486, the use of antiglucocorticoids to neutralize endogenous cortisol will be associated with a rise in ACTH and cortisol as the pituitary-adrenal axis responds to the functional decrease in cortisol as glucocorticoid receptors in these organs are blocked. Indeed, an effort to modulate the anti-inflammatory and immunosuppressive effects of endogenous cortisol with high doses of RU 486 using both humoral and cellular markers appeared to be unsuccessful, probably due to the compensatory increase in cortisol secretion.[40] Whether selective beneficial actions of low doses of glucocorticoid antagonists exist will have to be established by clinical trials for each condition for which they are proposed.

VII. Untoward Effects

Toxicological studies have been conducted in rats and monkeys for up to 6 months. The changes observed were due to the antihormonal properties of the drug.[134] High dose RU 486 administration during the first 18 days of life to neonatal male and female rats induces permanent changes in their reproductive system.[135] Side effects consequent to single dose administration of RU 486 in humans are extremely uncommon. Long-term administration of RU 486 in doses ranging from 100–200 mg/day are generally well tolerated. The most common side effect reported is fatigue which develops in the majority of the subjects.[38] Nausea, anorexia, and vomiting may also occur.[36–39] The fact that such symptoms improve with supportive therapy that includes glucocorticoids is not sufficient evidence to suggest glucocorticoid deficiency. Although hypoadrenalism consequent to glucocorticoid antagonism with RU 486 has been reported on occasion in long-term treatment with doses exceeding 200 mg/day, this has rarely been objectively proven and is an uncommon occurrence in humans with an intact pituitary-adrenal axis. Nevertheless, if the clinical picture does suggest hypoadrenalism, then glucocorticoid replacement is indicated.

Other side effects reported during long-term treatment include slight decrease in serum potassium, weight loss, cessation of menses in premenopausal women, intermittent hot flashes, transient thinning of the hair, development of Hashimoto's thyroiditis, and occasional decrease in

libido and gynecomastia in males.[32,36–38,124] The latter is presumably due to the fact that RU 486 binds with low affinity to androgen receptors.[8] Laue and co-workers[40] administered a high dose of RU 486 (10 mg/kg/day) to 11 normal males subjects. Eight developed generalized exanthem after 9 days of RU 486 treatment. This phenomenon has not been observed in the treatment of patients with Cushing's syndrome even with higher doses.[32] The hypercortisolemia characteristic of the latter condition may have a protective effect against this hypersensitivity reaction.

Since some women fail to abort and may continue with their pregnancy following RU 486 administration, is is important to determine if there are any teratogenic effects. None were observed in rats and rabbits.[134] However, in other studies in rabbits, skull deformities did occur and were attributed to mechanical effects secondary to uterine contractions because of the decrease in progesterone activity.[136] Experiments conducted on monkey embryos exposed in vivo and in vitro to RU 486 in the perinidatory interval showed no teratogenicity.[137]

There are isolated case reports of women who have taken RU 486 alone or in combination with prostaglandins, failed to abort, and have elected to continue with their pregnancy. Three normal births were reported in Britain[138] and one in France.[139] In another subject in France, pregnancy was terminated at 18 weeks because of an abnormal ultrasound. Severe fetal abnormalities were detected but pathologists did not conclude that RU 486 played a role in the genesis of these abnormalities.[139] However, prostaglandins including misoprostol have been reported to be teratogenic.[140,141] At the current state of knowledge, women who fail to abort following RU 486 should be warned about possible teratogenic effects and should be offered surgical abortion.

VIII. Conclusions

It has been estimated that worldwide, approximately 55 million pregnancies are terminated each year by abortion.[142] In those countries where abortions are illegal, many women still seek pregnancy termination from untrained individuals who do not use sterile operative procedures. Even in countries where abortion is legal, there is often a shortage of trained personnel and limited facilities. For this reason, abortion is performed in situations which are not ideal, resulting in maternal mortality approaching that in countries where abortion is illegal. Poorly performed abortion is responsible for 25% of maternal deaths in some countries. In addition, there is considerable morbidity due to infections and perforation of the uterus resulting from improper techniques. The availability of a safe and effective medical abortifacient would thus have a marked impact on maternal health throughout the world.[4]

In France, RU 486 plus misoprostol or gemeprost is approved for ending

pregnancies of up to 49 days in duration. It has been estimated that, in France, one-third of women who decide to interrupt an early pregnancy now choose this chemical approach over the standard surgical procedures[1] and over 120,000 women have now been treated (Ulmann, personal communication). In France, RU 486 and prostaglandin must be given in registered clinics under strict medical control. It can only be administered to French nationals or people with a minimum of 3 months' residence in France. A week's delay is necessary from the time of the initial interview until RU 486 administration. RU 486 is given no later than day 49 of amenorrhea and prostaglandin is administered 48 hours later with a surveillance in the clinic of 3–4 hours; there must be a follow-up visit after 5–9 days. Women must agree to accept surgical abortion in case of failure for fear of teratogenesis. As greater experience accumulates and as RU 486 is registered for sale in other countries in Europe, it is possible that these restrictions will be relaxed.

Currently, Roussel Uclaf insists that a country must meet five criteria before it will seek approval for marketing. Abortion must be legal; abortion must be accepted by medical, public and political opinion; a suitable synthetic prostaglandin must be available; distribution must be strictly controlled; and a patient must agree in writing that if RU 486-induced abortion fails, she will proceed with a surgical abortion.

In Britain, the method has also been officially approved since July 1991 for terminating pregnancy in women with amenorrhea of up to 9 weeks and RU 486 is used by approximately 500 women each month. The antiprogestin has also been recently approved for use in Sweden. Although Roussel Uclaf did register RU 486 in China in 1987, currently they are not supplying the drug. RU 486 has also been synthesized in China but, to our knowledge, no results of large trials have been reported (Ulmann, personal communication). It is highly likely that within the next few years, RU 486 will become available in many other countries where abortion is permitted. In developed countries, RU 486 offers women an alternative option to surgical abortion. In developing countries where surgical abortion is legal but poorly performed and not widely available, RU 486 could provide women their only option for safe abortion and thus markedly reduce maternal morbidity and mortality.

The reasons why antiprogestins are not available for medical abortion in the United States are complex. In part, it is due to the reluctance of large pharmaceutical companies to conduct research on abortion and market products for this purpose for some of the same reasons that they have reduced their efforts to develop new contraceptives. This is due in part to liability and lack of financial incentive. In addition, there has been concern about direct opposition from highly vocal conservative organizations that include former presidents of the United States. Even though these organizations have threatened to boycott pharmaceutical companies

that market abortifacients, there is no evidence to suggest boycotts of companies for such reasons have ever proven effective; however, many companies were afraid to oppose the US government. It is, therefore, not surprising that companies that have developed antiprogestins have been reluctant to introduce these agents into the US. Thus, the proximal reason that RU 486 and other antiprogestins are not available to women in this country is because no pharmaceutical company has elected to register such an agent with the FDA, not because of legislation preventing them from doing so. Furthermore, there are no laws that prohibit importation of RU 486 for clinical studies under approved INDs or for use by physicians to treat the general public if there were an approved application for marketing. In the US, political and financial expediency rather than the welfare of women is dictating the fate of RU 486 and other antiprogestins. With the recent change in government in the US, tension concerning the use of RU 486 should decrease.

RU 486 is currently the only antiprogestin to have been extensively evaluated in clinical trials. Since the original report on RU 486, over 400 compounds with potential antiprogestin activity have been synthesized and over 700 research reports or abstracts have been published.[143] With some of the new compounds, the antiprogestin and antiglucocorticoid activities have been dissociated. If abortion is the only use that can be found for antiprogestins, then few of these agents will be developed for clinical use. The demonstration that antiprogestins have a variety of uses for treatment of both benign and neoplastic disorders would make it financially feasible to register many of these agents.

In spite of the advances that have been made with RU 486, there are still many unanswered questions with regard to its use. Even when administered under the best circumstance, i.e., pregnancies with amenorrhea of under 7–9 weeks' duration together with prostaglandins, the success rate for complete abortion is 95%. Therefore, some women still fail to respond, and will need a follow-up surgical procedure. Thus, research needs to be directed to improving the effectiveness and broadening the window of time when RU 486 can be used.

In addition, studies to optimize type, dose, and route of administration of the prostaglandin analog need to be completed. An urgent requirement is the introduction of a prostaglandin analog stable at room temperature and devoid of adverse cardiovascular effects. It is possible that misoprostol, an agent recently approved in France, may fulfill this need. A prostaglandin derivative exerting a delayed effect, which could be administered at the same time as RU 486, would make one visit possible and thus ease the burden of women who find it difficult to make multiple trips to the clinic.

Extensive efforts should be undertaken to exploit the other indications for RU 486. Recently, this antiprogestin has also been approved in France as an adjunct to prostaglandins for the medical termination of first and

second trimester pregnancies, as well as for the expulsion of uterine contents following fetal death. In view of the very promising results obtained to date, further large studies need to be conducted to determine the efficacy and acceptability of RU 486 as a postcoital agent.

Additional studies have to be undertaken to determine how RU 486 and other antiprogestins can be combined with other agents for use as a once-a-month menses regulator or as a contraceptive either by inhibiting ovulation or by disturbing the integrity of the endometrium without interfering with hormonal or bleeding events of the cycle. Furthermore, there is a need to undertake additional studies to evaluate other gynecological, antitumor, and antiglucocorticoid uses of this fascinating group of drugs. The availability of RU 486 has made it possible to elucidate the actions of glucocorticoids and progesterone in physiological, as well as pathological states. The demonstration of the diverse agonistic and antagonistic actions of RU 486 on the uterus and on mammary tumor cells suggest that uses may be found for this class of drugs beyond those envisioned when they were first proposed as medical abortifacients.

Acknowledgments

This study was supported by The George J. Hecht Fund, The Andrew W. Mellon Foundation, The Rockefeller Foundation, The Fred H. Bixby Foundation, The Buffett Foundation, The Educational Foundation of America, The Moore-White Medical Foundation, The Edward John Noble Foundation, The Playboy Foundation, and The Swedish International Development Authority. We thank Prof. I. Agranat, Hebrew University, and Dr. O. Heikinheimo, University of Finland, for their helpful comments, and Ms. Linda McKeiver for her assistance in preparing the manuscript.

References

1. Ulmann A, Teutsch G, Philibert D. RU 486. Sci Amer 1990; 262: 42–8.
2. Baulieu EE. Contragestion and other clinical applications of RU 486, an antiprogesterone at the receptor. Science 1989; 245: 1351–7.
3. Spitz IM, Bardin CW. Clinical applications of the antiprogestin RU 486. Endocrinologist 1993; 3: 58-66.
4. Spitz IM, Bardin CW. RU 486—A modulator of progestin and glucocorticoid action. N Engl J Med 1993; 404–12.
5. Sherman MR, Corvol PL, O'Malley BW. Progesterone-binding components of chick oviduct. 1. Preliminary characterization of cytoplasmic components. J Biol Chem 1970; 245: 6085–96.
6. Hoff JD, Quigley ME, Yen SSC. Hormonal dynamics at mid cycle: areevaluation. J Clin Endocrinol Metab 1983; 57: 792–796.
7. Philibert D, Deraedt R, Teutsch G. VIII Int Cong of Pharmacology. 1981; Abst. No. 1463.
8. Philibert D. RU 38486: an original multifaceted antihormone in vivo. In:

Adrenal Steroid Antagonism. MK Agarwal, ed. Berlin: Walter de Gruyter and Co, 1984: 77–101.
9. Evans RM. The steroid and thyroid hormone receptor superfamily. Science 1988; 240: 889–95.
10. Teutsch G. Analogues of RU 486 for the mapping of the progestin receptor: synthetic and structural aspects. EE Baulieu, SJ Segal, eds. In: The Antiprogestin Steroid RU 486 and Human Fertility Control. New York: Plenum Press, 1985: 27–47.
11. Wiechert R, Neef G. Synthesis of antiprogestational steroids. J Steroid Biochem 1987; 27 : 851–8.
12. Benhamou B, Garcia T, Lerouge T, Vergezac A, Gofflo D, Bigogne C, Chambon P, Gronemeyer H. A single amino acid that determines the sensitivity of progesterone receptors to RU 486. Science 1992; 255: 206–9.
13. El-Ashry D, Onate SA, Nordeen SK, Edwards DP. Human progesterone receptor complexed with the antagonist RU 486 binds to hormone response elements in a structurally altered form. Mol Endocrinol 1989s; 3: 1545–58.
14. Bagchi MK, Tsai SY, Tsai M-J, O'Malley BW. Identification of a functional intermediate in receptor activation in progesterone-dependent cell-free transcription. Nature 1990; 345: 547–50.
15. Deraedt R, Bonnat C, Busigny M, Chatelet P, Cousty C, Mouren M, Philibert D, Pottier J, Salmon J. Pharmacokinetics of RU 486. EE Baulieu, SJ Segal, eds. In: The Antiprogestin Steroid RU 486 and Human Fertility Control. New York: Plenum Press, 1985: 103–122.
16. van Uem JFHM, Hsiu JG, Chillik CF, Danforth DR, Ulmann A, Baulieu EE, Hodgen GD. Contraceptive potential of RU 486 by ovulation inhibition: I. Pituitary versus ovarian action with blockade of estrogen-induced endometrial proliferation. Contraception 1989; 40: 171–84.
17. Heikinheimo O, Croxatto H, Salvatierra AM, Chang CC, Luukkainen T, Lähteenmäki P. Intravaginal administration of RU 486 in humans and rats: inadequate absorption in humans. Human Reprod 1987; 2: 645–8.
18. Steingold KA, Matt DW, Dua L, Anderson TL, Hodgen GD. Orosomucoid in human pregnancy serum diminishes bioavailability of the progesterone antagonist RU 486 in rats. Am J Obstet Gynecol 1990; 162: 523–24.
19. Lähteenmäki P, Heikinheimo O, Croxatto H, Spitz I, Shoupe D, Birgerson L, Luukkainen T. Pharmacokinetics and metabolism of RU 486. J Steroid Biochem 1987; 27: 859–63.
20. Shoupe D, Mishell Jr DR, Lähteenmäki P, Heikinheimo O, Birgerson L, Madkour H, Spitz IM. Effects of the antiprogesterone RU 486 in normal women. I. Single-dose administration in the midluteal phase. Am J Obstet Gynecol 1987; 157: 1415–20.
21. Heikinheimo O, Kontula K, Croxatto H, Spitz I, Luukkainen T, Lähteenmäki P. Plasma concentrations and receptor binding of RU 486 and its metabolites in humans. J Steroid Biochem 1987; 26: 279–84.
22. Heikinheimo O, Haukkamaa M, Lähteenmäki P. Distribution of RU 486 and its demethylated metabolites in humans. J Clin Endocrinol Metab 1989; 68: 270–5.
23. Kelly RW, Healy DL, Cameron MJ, Cameron IT, Baird DT. The stimulation

of prostaglandin production by two antiprogesterone steroids in human endometrial cells. J Clin Endocrinol Metab 1986; 62: 1116–23.

24. Smith SK, Kelly RW. The effect of the antiprogestins RU 486 and ZK 98734 on the synthesis and metabolism of prostaglandins $F2_{\alpha}$ and E_2 in separated cells from early human decidua. J Clin Endocrinol Metab 1987; 65: 527–34.
25. Frydman R, Taylor S, Ulmann A. Transplacental passage of mifepristone. Lancet 1985; ii: 1252.
26. Hill NCW, Selinger M, Ferguson J, MacKenzie IZ. The placental transfer of mifepristone (RU 4860) during the second trimester and its influence upon maternal and fetal steroid concentrations. Brit J Obstet Gynaecol 1990; 97: 406–11.
27. Wolf JP, Chillik CF, Itskovitz J, Weyman D, Anderson TL, Ulmann A, Baulieu EE, Hodgen GD. Transplacental passage of a progesterone antagonist in monkeys. Am J Obstet Gynecol 1988; 159: 238–42.
28. Gaillard RC, Poffet D, Riondel AM, Saurat J-H. RU 486 inhibits peripheral effects of glucocorticoids in humans. J Clin Endocrinol Metab 1985; 61: 1009–11.
29. Gaillard RC, Riondel A, Muller AF, Herrmann W, Baulieu EE. RU 486: a steroid with antiglucocorticosteroid activity that only disinhibits the human pituitary-adrenal system at a specific time of day. Proc Natl Acad Sci USA 1984; 81: 3879–82.
30. Shoupe D, Mishell Jr DR, Brenner PF, Spitz IM. Pregnancy termination with a high and medium dosage regimen of RU 486. Contraception 1986; 33: 455–61.
31. Mishell Jr DR, Shoupe D, Brenner PF, Lacarra M, Horenstein J, Lähteenmäki P, Spitz IM. Termination of early gestation with the anti-progestin steroid RU 486: Medium versus low dose. Contraception 1987; 35: 307–21.
32. Chrousos GP, Laue L, Nieman LK, Udelsman R, Kawai S, Loriaux DL. Clinical applications of RU 486, a prototype glucocorticoid and progestin antagonist. F Mantero, R Takeda, BA Scoggins, EG Biglieri and JW Funder, eds. In: The Adrenal and Hypertension: From Cloning to Clinic. New York: Raven Press, 1989: 273–84.
33. Spitz IM, Wade CE, Krieger DT, Lähteenmäki P, Bardin CW. Effect of RU 486 on the pituitary-adrenal axis in the dog. EE Baulieu and SJ Segal, eds. In: The Antiprogestin Steroid RU 486 and Human Fertility Control. New York: Plenum Publishing Corp, 1985: 315–9.
34. Li T-C, Dockery P, Thomas P, Rogers AW, Lenton EA, Cooke ID. The effects of progesterone receptor blockade in the luteal phase of normal fertile women. Fertil Steril 1988; 50: 732–42.
35. Kettel LM, Murphy AA, Mortola JF, Liu JH, Ulmann A, Yen SS. Endocrine responses to long-term administration of the antiprogesterone RU 486 in patients with pelvic endometriosis. Fertil Steril 1991; 56: 402–6.
36. Bakker GH, Setyono-Han B, Portengen H, de Jong FH, Foekens JA, Klijn JGM. Treatment of breast cancer with different antiprogestins: Preclinical and clinical studies. J Steroid Biochem Molec Biol 1990; 37: 789–94.
37. Klijn JGM, de Jong FH, Bakker G H, Lamberts S W J, Rodenburg CJ, Alexieva-Figusch J. Antiprogestins, a new form of endocrine therapy for human breast cancer. Cancer Res 1989; 49: 2851–6.

38. Grunberg SM, Weiss MH, Spitz IM, Ahmadi J, Sadun A, Russell CA, Lucci L, Stevenson LL. Treatment of unresectable meningiomas with the antiprogesterone agent mifepristone. J Neurosurg 1991; 74: 861–6.
39. Lamberts SWJ, Koper JW, de Jong FH. The endocrine effects of long-term treatment with mifepristone (RU 486). J Clin Endocrinol Metab 1991; 73: 187–91.
40. Laue L, Lotze MT, Chrousos G P, Barnes K, Loriaux DL, Fleisher TA. Effect of chronic treatment with the glucocorticoid antagonist RU 486 in man: toxicity, immunological, and hormonal aspects. J Clin Endocrinol Metabol 1990; 71: 1474–80.
41. Laue L, Chrousos GP, Loriaux DL, Barnes K, Munson P, Nieman L, Schaison G. The antiglucocorticoid and antiprogestin steroid RU 486 suppresses the adrenocorticotropin response to ovine corticotropin releasing hormone in man. J Clin Endocrinol Metab 1988; 66: 290–3.
42. Laue L, Gallucci W, Loriaux DL, Udelsman R, Chrousos GP. The antiglucocorticoid and antiprogestin steroid RU 486: its glucocorticoid agonist effect is inadequate to prevent adrenal insufficiency in primates. J Clin Endocrinol Metab 1988; 67 : 602–6.
43. Swahn ML, Bygdeman M, Cekan S, Xing S, Masironi B, Johannisson E. The effect of RU 486 administered during the early luteal phase on bleeding pattern, hormonal parameters and endometrium. Human Reprod 1990; 5: 402–8.
44. Berthois Y, Salat-Baroux J, Cornet D, de Brux J, Kopp F, Martin PM. A multiparametric analysis of endometrial estrogen and progesterone receptors after the postovulatory administration of mifepristone. Fertil Steril 1991; 55: 547–54.
45. Swahn ML, Johannisson E, Daniore V, de la Torre B, Bygdeman M. The effect of RU 486 administered during the proliferative and secretory phase of the cycle on the bleeding pattern, hormonal parameters and the endometrium. Human Reprod 1988; 3: 915–21.
46. Gravanis A, Schaison G, George M, de Brux J, Satyaswaroop PG, Baulieu EE, Robel P. Endometrial and pituitary responses to the steroidal antiprogestin RU 486 in postmenopausal women. J Clin Endocrinol Metab 1985; 60: 156–63.
47. Koering MJ, Healy DL, Hodgen GD. Morphologic response of endometrium to a progesterone receptor antagonist, RU 486, in monkeys. Fertil Steril 1986; 45: 280–7.
48. Wolf JP, Ulmann A, Hsiu JG, Baulieu EE, Anderson TL, Hodgen GD. Noncompetitive antiestrogenic effect of RU 486 in blocking the estrogen-stimulated luteinizing hormone surge and the proliferative action of estradiol on endometrium in castrate monkeys. Fertil Steril 1989; 52: 1055–60.
49. Hsueh AJW, Peck EJ, Clark JH. Progesterone antagonism of the oestrogen receptor and oestrogen-induced uterine growth. Nature 1975; 254: 337–9.
50. Haluska GJ, West NB, Novy MJ, Brenner RM. Uterine estrogen receptors are increased by RU 486 in late pregnant Rhesus Macaques but not after spontaneous labor. J Clinical Endocrinol Metab 1990; 70: 181–6.
51. Garcia E, Bouchard P, de Brux J, Berdah J, Frydman R, Schaison G, Milgrom E, Perrot-Applanat M. Use of immunocytochemistry of progesterone and

estrogen receptors for endometrial dating. J Clin Endocrinol Metab 1988; 67: 80–7.

52. Neulen J, Williams RF, Hodgen GD. RU 486 (mifepristone): induction of dose–dependent elevations of estradiol receptor in endometrium from ovariectomized monkeys. J Clin Endocrinol Metab 1990; 71: 1074–75.
53. Garzo VG, Liu J, Ulmann A, Baulieu EE, Yen SSC. Effects of an antiprogesterone (RU 486) on the hypothalamic-hypophyseal-ovarian-endometrial axis during the luteal phase of the menstrual cycle. J Clin Endocrinol Metab 1988; 66: 508–7.
54. Nieman LK, Choate TM, Chrousos GP, Healy DL, Morin M, Renquist D, Merriam GR, Spitz IM, Bardin CW, Baulieu EE, Loriaux DL. The progesterone antagonist RU 486. A potential new contraceptive agent. N Engl J Med 1987; 316: 187–91.
55. Croxatto HB, Salvatierra AM, Croxatto HD, Spitz IM. Variable effects of RU 486 on endometrial maintenance in the luteal phase extended by exogenous hCG. Clin Endocrinol 1989; 31: 15–23.
56. Wolf JP, Danforth DR, Ulmann A, Baulieu EE, Hodgen GD. Contraceptive potential of RU 486 by ovulation inhibition. II. Suppression of pituitary gonadotropin secretion in vitro. Contraception 1989; 40: 185–93.
57. Lee W-S, Smith MS, Hoffman GE. Progesterone enhances the surge of luteinizing hormone by increasing the activation of luteinizing hormone-releasing hormone neurons. Endocrinology 1990; 127: 2604–6.
58. Collins RL, Hodgen GD. Blockage of the spontaneous midcycle gonadotropin surge in monkeys by RU 486: a progesterone antagonist or agonist? J Clin Endocrinol Metab 1986; 63: 1270–76.
59. Shoupe D, Mishell Jr DR, 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.
60. Permezel JM, Lenton EA, Roberts I, Cooke ID. Acute effects of progesterone and the antiprogestin RU 486 on gonadotropin secretion in the follicular phase of the menstrual cycle. J Clin Endocrinol Metab 1989; 68: 960–5.
61. Stuenkel CA, Garzo VG, Morris S, Liu JH, Yen SSC. Effects of the antiprogesterone RU 486 in the early follicular phase of the menstrual cycle. Fertil Steril 1990; 53: 642–6.
62. Liu JH, Garzo G, Morris S, Stuenkel C, Ulmann A, Yen SSC. Disruption of follicular maturation and delay of ovulation after administration of the antiprogesterone RU 486. J Clin Endocrinol Metab 1987; 65: 1135–40.
63. Murphy AA, Kettel LM, Morales AJ, Roberts VJ, Yen SSC. Regression of uterine leiomyomata in response to the antiprogesterone RU 486. J Clin Endoc Metab 1993; 76: 513–7.
64. Healy DL, Chrousos GP, Schulte HM. Pituitary and adrenal responses to the antiprogesterone and antiglucocorticoid steroid RU 486 in primates. J Clin Endocrinol Metab 1983; 5: 863.
65. Swahn ML, Ugocsai G, Bygdeman M, Kovacs L, Belsey EM, Van Look PFA. Effect of oral prostaglanding E_2 on uterine contractility and outcome of treatment in women receiving RU 486 (mifepristone) for termination of pregnancy. Human Reprod 1989; 4: 21–8.

66. Das C, Catt KJ. Antifertility actions of the progesterone antagonist RU 486 include direct inhibition of placental hormone secretion. Lancet 1987; ii: 599–601.
67. Csapo AI. The prospects of PGs in postconceptional therapy. Prostaglandins 1973; 3: 245–89.
68. Norman JE, Wu WX, Kelly RW, Glassier AF, McNeilly AS, Baird DT. Effects of mifepristone in vivo on decidual prostaglandin synthesis and metabolism. Contraception 1991; 44: 89–98.
69. Cheng L, Kelly RW, Thong KJ, Hume R, Baird DT. The effects of mifepristone (RU486) on prostaglandin dehydrogenase in decidual and chorionic tissue in early pregnancy. Human Reproduction 1993; 8: 705–9.
70. Norman JE, Kelly RW, Baird DT. Uterine activity and decidual prostaglandin production in women in early pregnancy in response to mifepristone with or without indomethacin in vivo. Human Reprod 1991; 6: 740–4.
71. Bygdeman M, Swahn ML. Progesterone receptor blockage. Effect on uterine contractility and early pregnancy. Contraception 1985; 32: 45–51.
72. Radestad A, Bygdeman M, Green K. Induced cervical ripening with mifepristone (RU 486) and bioconversion of arachidonic acid in human pregnant uterine cervix in the first trimester. Contraception 1990; 41: 283–92.
73. Urquhart DR, Templeton AA. Mifepristone (RU 486) for cervical priming prior to surgically induced abortion in the late first trimester. Contraception 1990; 42 : 191–9.
74. Gupta JK, Johnson N. Effect of mifepristone on dilatation of the pregnant and non-pregnant cervix. Lancet 1990; 335: 1238–40.
75. DiMattina M, Albertson B, Seyler DE, Loriaux DL, Falk RJ. Effect of the antiprogestin RU 486 on progesterone production by cultured human granulosa cells: inhibition of the ovarian 3 β-hydroxysteroid dehydrogenase. Contraception 1986; 34: 199–206.
76. Parinaud J, Perret B, Ribbes H, Vieitez G, Baulieu EE. Effects of RU 486 on progesterone secretion by human preovulatory granulosa cells in culture. J Clin Endocrinol Metab 1990; 70: 1534–7.
77. Batista MC, Cartledge TP, Zellmer AW, Nieman LK, Merriam GR, Loriaux DL. Evidence for a critical role of progesterone in the regulation of the midcycle gonadotropin surge and ovulation. J Clin Endocrinol Metab 1992; 74: 565–70.
78. Herrmann W, Wyss R, Riondel A, Philibert D, Teutsch G, Sakiz E, Baulieu EE. Effet d'un steroide antiprogesterone chez la femme: Interruption du cycle menstruel et de la grossesse au debut. CR Acad Sci Paris 1982; 294: 933–8.
79. Birgerson L, Odlind V. The antiprogestational agent RU 486 as an abortifacient in early human pregnancy: a comparison of three dose regimens. Contraception 1988; 38: 391–400.
80. Couzinet B, Le Strat N, Ulmann A, Baulieu EE, Schaison G. Termination of early pregnancy by the progesterone antagonist, RU 486 (mifepristone). N Engl J Med 1986; 315: 1565–70.
81. Vervest HAM, Haspels AA. Preliminary results with the antiprogestational compound RU-486 (mifepristone) for interruption of early pregnancy. Fertil Steril 1985; 44: 627–32.

82. Chillik CF, Hsiu JG, Acosta AA, van Uem JFHM, Hodgen GD. RU 486–induced menses in cynomolgus monkeys: uniformity of endometrial sloughing. Fertil Steril 1986; 45: 708–12.
83. Li TC, Lenton EA, Dockery P, Rogers AW, Cooke ID. Why does RU 486 fail to prevent implantation despite success in inducing menstruation?. Contraception 1988; 38: 401–6.
84. Grimes DA, Bernstein GS, Lacarra M, Shoupe D, Mishell Jr DR. Predictors of failed attempted abortion with the antiprogestin mifepristone (RU 486). Am J Obstet Gynecol 1990; 162: 910–7.
85. Spitz IM, Heikinheimo O, Wade CE. The divergent effect of RU 486 on adrenal function in the dog is related to differences in its pharmacokinetics. Acta Endocrinol 1993; 128: 459–65.
86. Heikinheimo O, Ylikorkala O, Turpeinen U, Lähteenmäki P. Pharmacokinetics of the antiprogesterone RU 486: no correlation to clinical performance of RU 486. Acta Endocrinol 1990; 123: 298–304.
87. Silvestre L, Dubois C, Renault M, Rezvani Y, Baulieu EE, Ulmann A. Voluntary interruption of pregnancy with mifepristone (RU 486) and a prostaglandin analogue. N Engl J Med 1990; 322: 645–8.
88. Ulmann A, Silvestre L, Chemma L, Rezvani Y, Renault M, Aguillaume CJ, Baulieu EE. Medical termination of early pregnancy with mifepristone (RU 486) followed by a prostaglandin analogue. Acta Obstet Gynecol Scand 1992; 71: 278–83.
89. Multicentre Trial UK. The efficacy and tolerance of mifepristone and prostaglandin in first trimester termination of pregnancy. Br J Obstet Gynaecol 1990; 97: 480–6.
90. Cameron IT, Baird DT. Early pregnancy termination: a comparison between vaccum aspiration and medical abortion using prostaglandin (16, 16 dimethyl-trans-Δ_2-PGE$_1$ methylester) or the antiprogestogen RU 486. Brit J Obstet Gyn 1988; 95: 271–6.
91. Klitsch M. Antiprogestin and the abortion controversy. A progress report. Fam Plan Perspectives 1991; 23: 275–81.
92. Hill NCW, Ferguson J, MacKenzie IZ. The efficacy of oral mifepristone (RU 38,486) with a prostaglandin E$_1$ analog vaginal pessary for the termination of early pregnancy: complications and patient acceptability. Am J Obstet Gynecol 1990; 162: 414–7.
93. Rodger MW, Logan AF, Baird DT. Induction of early abortion with mifepristone (RU 486) and two different doses of prostaglandin pessary (gemeprost). Contraception 1989; 39: 497–502.
94. Rodger MW, Baird DT. Blood loss following induction of early abortion using mifepristone (RU 486) and a prostaglandin analogue (gemeprost). Contraception 1989; 40: 439–47.
95. Norman JE, Thong KJ, Baird DT. Uterine contractility and induction of abortion in early pregnancy by misoprostol and mifepristone. Lancet 1991; 338: 1233–6.
96. Peyron R, Aubeny E, Targosz V, Silvestre L, Renault M, Elkik F, Leclerc P, Ulmann A, Baulieu EE. Early pregnancy interruption with mifepristone (RU 486) and the orally active prostaglandin misoprostol. New Engl J Med 1993 (in press).

97. Thong KJ, Baird DT. Induction of abortion with mifepristone and misoprostol in early pregnancy. Br J Obstet Gynaecol 1992; 99: 1004–7.
98. Luukkainen T, Heikinheimo O, Haukkamaa M, Lähteenmäki P. Inhibition of folliculogenesis and ovulation by the antiprogesterone RU 486. Fertil Steril 1988; 49: 961–3.
99. Ledger WL, Sweeting VM, Hillier H, Baird DT. Inhibition of ovulation by low-dose mifeprostone (RU 486). Human Reprod 1992; 7: 6.
100. Croxatto HB, Salvatierra AM, Croxatto HD, Fuentealba A. Effects of continuous treatment with low dose mifepristone throughout one menstrual cycle. Human Reprod 1993; 8: 201–7.
101. Kekkonen R, Henrik A, Haukkamaa M, Heikinheimo O, Luukkainen T, Lähteenmäki P. Interference with ovulation by sequential treatment with the antiprogesterone RU 486 and synthetic progestin. Fertil Steril 1990; 53: 747–50.
102. Danforth DR, Dubois C, Ulmann A, Baulieu EE, Hodgen GD. Contraceptive potential of RU 486 by ovulation inhibition. III. Preliminary observations on once weekly oral administration. Contraception 1989; 40: 195–200.
103. Spitz IM, Croxatto HB, Salvatierra AM, Heikinheimo O. Response to intermittent RU 486 in normal women. Fertil Steril 1993; 59: 971–5.
104. Greene KE, Kettel LM, Yen SSC. Interruption of endometrial maturation without hormonal changes by an antiprogesterone during the first half of luteal phase of the menstrual cycle: A contraceptive potential. Fertil Steril 1992; 58: 338–43.
105. Swahn ML, Gemzell K, Bygdeman M. Contraception with mifepristone. Lancet 1991; 338: 942–3.
106. Croxatto HB, Salvatierra AM, Romero C, Spitz IM. Late luteal phase administration of RU 486 for three successive cycles does not disrupt bleeding patterns of ovulation. J Clin Endocrinol Metab 1987; 65: 1272–7.
107. Roseff SJ, Kettel LM, Rivier J, Burger HG, Baulieu EE, Yen SSC. Accelerated dissolution of luteal-endometrial integrity by the administration of antagonists of gonadotropin-releasing hormone and progesterone to late luteal phase women. Fertil Steril 1990; 54: 805–10.
108. Lähteenmäki P, Rapeli T, Kääriäinen M, Alfthan H, Ylikorkala O. Late postcoital treatment against pregnancy with antiprogesterone RU 486. Fertil Steril 1988; 50: 36–8.
109. van Santen MR, Haspels AA. Interception IV: Failure of mifepristone (RU 486) as a monthly contragestive, "Lunarette". Contraception 1987; 35: 433–8.
110. Ulmann A. Uses of RU 486 for contragestion: an update. Contraception 1987; 36: (suppl): 27–31.
111. Dubois C, Ulmann A, Baulieu EE. Contragestion with late luteal administration of RU 486 (mifepristone). Fertil Steril 1988; 50: 593–6.
112. Couzinet B, Strat NL, Silvestre L, Schaison G. Late luteal administration of the antiprogesterone RU 486 in normal women: effects on the menstrual cycle events and fertility control in a long-term study. Fertil Steril 1990; 54: 1039–44.
113. Webb AMC. Alternative treatments in oral postcoital contraception: interim results. Adv Contracept 1991; 7: 271–9.
114. Glasier A, Thong KJ, Dewar M, Mackie M, Baird DT. Mifepristone (RU

486) compared with high-dose estrogen and progestogen for emergnecy postcoital contraception. N Engl J Med 1992; 327: 1041–4.
115. Henshaw RC, Templeton AA. Pre-operative cervical preparation before first trimester vacuum aspiration: a randomized controlled comparison between gemeprost and mifepristone (RU 486). Brit J Obstet Gynecol 1991; 98: 1025–30.
116. Rodger MW, Baird DT. Pretreatment with mifepristone (RU 486) reduces interval between prostaglandin administration and expulsion in second trimester abortion. Brit J Obstet Gyn 1990; 97: 41–5.
117. Cabrol D, Dubois C, Cronje H, Gonnet JM, Guillot M, Maria B, Moodley J, Oury JF, Thoulon JM, Treisser A, Ulmann D, Correl S, Ulmann A. Induction of labor with mifepristone (RU 486) in intrauterine fetal death. Am J Obstet Gynecol 1990; 163: 540–2.
118. Asch RH, Weckstein LN, Balmaceda JP, Rojas F, Spitz IM, Tadir Y. Nonsurgical expulsion of non-viable early pregnancy: a new application of RU 486. Human Reprod 1990; 5: 481–3.
119. Haluska GJ, Stanczyk FZ, Cook MJ, Novy MJ. Temporal changes in uterine activity and prostaglandin response to RU 486 in rhesus macaques in late gestation. Am J Obstet Gynecol 1987; 157: 1487–95.
120. Wolf JP, Sinosich M, Anderson TL, Ulmann A, Baulieu EE, Hodgen GD. Progesterone antagonist (RU 486) for cervical dilation, labor induction, and delivery in monkeys: effectiveness in combination with oxytocin. Am J Obstet Gynecol 1989; 160: 45–6.
121. Frydman R, Baton C, Lelaidier C, Vial M, Bourget Ph, Fernandez H. Mifepristone for induction of labour. Lancet 1991; 337: 488–9.
122. Bardon S, Vignon F, Chalbos D, Rochefort H. RU 486, a progestin and glucocorticoid antagonist, inhibits the growth of breast cancer cells via the progesterone receptor. J Clin Endocrinol Metab 1984; 60: 692–7.
123. Horwitz KB. The antiprogestin RU38,486: receptor-mediated progestin versus antiprogestin actions screened in estrogen-insensitive T47D_{co} human breast cancer cells. Endocrinology 1985; 116: 2236–45.
124. Romieu G, Maudelonde T, Ulmann A, Pujol H, Grenier J, Cavalie G, Khalaf S, Rochefort H. The antiprogestin RU 486 in advanced breast cancer: Preliminary clinical trial. Bull Cancer 1987; 74: 455–61.
125. Blankenstein MA, Van der Meulen-Dijk C, Thijsson LHH. Assay of oestrogen and progestrin receptors in human meningioma cytosis using immuological methods. Clin Chim Acta 1987; 165: 189–5.
126. Olson JJ, Beck DW, Schlechte J, Loh PM. Hormonal manipulation of meningiomas in vitro. J Neurosurg 1986; 65: 99–107.
127. Olson JJ, Beck DW, Schlechte JA, Loh PM. Effect of the antiprogesterone RU-38486 on meningioma implanted into nude mice. J Neurosurg 1987; 66: 584–7.
128. Alford TC, Do HM, Geelhoed GW, Tsangaris NT, Lippman ME. Steroid hormone receptors in human colon cancers. Cancer 1979; 43: 980–4.
129. Nieman LK, Chrousos GP, Kellner C, Spitz IM, Nisula BC, Cutler GB, Merriam GR, Bardin CW, Loriaux DL. Successful treatment of Cushing's syndrome with the glucocorticoid antagonist RU 486. J Clin Endocrinol Metab 1985; 61: 536–40.

130. Phillips CI, Gore SM, Green K, Cullen PM, Campbell M. Eye drops of RU 486–6, a peripheral steroid blocker, lower intraocular pressure in rabbits. Lancet 1984; i: 767–8.
131. Konagaya M, Bernard PA, Max SR. Blockage of glucocorticoid receptor binding and inhibition of dexamethasone-induced muscle atrophy in the rat by RU38486, a potent glucocorticoid antagonist. Endocrinology 1986; 119: 375–80.
132. Konagaya M, Max SR. A possible role for endogenous glucocorticoids in orchiectomy-induced atrophy of the rat levator ani muscle: studies with RU38486, a potent and selective antiglucocorticoid. J Steroid Biochem 1986; 25: 305–8.
133. Regelson W, Loria R, Kalimi M. Beyond 'Abortion': RU-486 and the needs of the crisis constituency. JAMA 1990; 264: 1026–7.
134. Deraedt R, Vannier B, Fournex R. Toxicological study on RU 486. EE Baulieu and SJ Segal, eds. In: The Antiprogestin Steroid RU 486 and Human Fertility Control. New York: Plenum Press, 1985: 123–66.
135. van der Schoot P, Baumgarten R. Effects of treatment of male and female rats in infancy with mifepristone on reproductive function in adulthood. J Reprod Fertil 1990; 90: 255–66.
136. Jost A. Animal reproduction. New data on the hormonal requirement of the pregnant rabbit: partial pregnancies and fetal anomalies resulting from treatment with a hormonal antagonist, given at a sub-abortive dosage. CR Acad Sci Paris 1986; 303 Serie 111: 281–4.
137. Wolf JP, Chillik CF, Dubois C, Ulmann A, Baulieu EE, Hodgen GD. Tolerance of perinidatory primate embryos to RU 486 exposure in vitro and in vivo. Contraception 1990; 41: 85–92.
138. Lim BH, Lees DAR, Bjornsson S, Lunan CB, Cohn MR, Stewart P, Davey A. Normal development after exposure to mifepristone in early pregnancy. Lancet 1990; 336: 257–8.
139. Pons J-C, Imbert M-C, Elefant E, Roux C, Herschkorn P, Papiernik E. Development after exposure to mifepristone in early pregnacy. Lancet 1991; 338: 763.
140. Collins FS, Mahoney MJ. Hydrocephalus and abnormal digits after failed first-trimester prostaglandin abortion attempt. J Pediatrics 1983; 102: 620–1.
141. Fonseca W, Alencar AJC, Mota FSB, Coelho HLL. Misoprostol and congenital malformations. Lancet 1991; 338: 56–142. Tietze C. Induced abortion: a world review. In: Population Council Fact Book. New York: The Population Council, 1983.
143. Hodgen GD. Antiprogestins: The political chemistry of RU 486. FEA Sienl 1991; 56: 394–9.