Contragestion and Other Clinical Applications of RU 486, an Antiprogesterone at the Receptor

ETIENNE-EMILE BAULIEU

RU 486, a steroid with high affinity for the progesterone receptor, is the first available active antiprogesterone. It has been used successfully as a medical alternative for early pregnancy interruption, and it also has other potential applications in medicine and for biochemical and pathophysiological endocrine research.

IN WOMEN, THE STEROID HORMONE PROGESTERONE (P) PLAYS a central role in the establishment and the maintenance of pregnancy (*1*). During the second part or luteal phase of the menstrual cycle, after ovulation, and during pregnancy (Fig. 1), P is essential for reproductive function (*2*). In the uterus, P causes the endometrium (internal lining) to undergo decidualization, which involves epithelial, glandular, mesenchymal, and vascular cells. These changes are necessary for implantation of the embryo (blastocyst), which occurs during the second week after fertilization. P also helps decrease the responsiveness of the smooth muscle of the uterus (myometrium) to contractile, excitatory agents such as prostaglandins or oxytocin; it also firms the cervix of the uterus and favors the formation of a mucous plug. All these effects are vital to the protection of the developing embryo and fetus. The function of P in the fallopian tubes, vagina, ovaries, and breasts is less well understood. Some cells in the central nervous system, particularly in the hypothalamus, are also targets for P.

P acts on target cells by way of the progesterone receptor (PR), a hormone binding protein obligatorily involved in the cellular response. PR concentration is increased in target cells by the preovulatory surge of estrogen. These cells are thus primed to respond to P subsequent to ovulation, when P is secreted by the corpus luteum. The corpus luteum is partly under the control of pituitary luteinizing hormone (LH) during the cycle, and its life span is remarkably constant (14 days) if it is not rescued by an additional stimulating hormone (gonadotropin). The functional demise of the corpus luteum (luteolysis) is associated with a rapid decrease of P and estradiol, and the endometrium undergoes disintegration and is shed (menstruation). If a fertilized ovum implants, human chorionic gonadotropin (hCG), produced by embryonic chorionic cells, ensures the prolongation of the life span of the corpus luteum and continued secretion of P. After about 9 weeks, the placenta takes over this function, and there is a decrease of hCG, while placental P production increases until the end of pregnancy. Increased plasma P concentrations are responsible for the lack of ovulation during pregnancy, presumably operating, via negative feedback, on the hypothalamus-pituitary LH release system. This inhibitory effect of P is the basis of current oral contraceptives, which contain a synthetic P analog (a progestin).

P is also involved earlier in the cycle, in follicle development, and in the process of ovulation. Folliculogenesis depends in part on intraovarian P, which is not secreted into the blood but is active locally in a paracrine or autocrine manner. The control of ovulation is poorly understood in the human. A small increase of blood P levels occurs before ovulation and reinforces the positive feedback effect of estradiol in the triggering of the midcycle LH surge. This P increment may also have direct effects on the follicle.

Progesterone Antagonists and Fertility Control

Encouraged in the late 1960s by the late Gregory Pincus, the "father" of the contraceptive pill, and the Ford Foundation to participate in the worldwide efforts to improve birth control methods, I found little evidence of major research directed toward the development of a drug that might decrease P activity at target cells.

Interruption of P synthesis or elimination of circulating P did not seem suitable or possible in women (*3*). The concept of achieving antagonism at the target tissue did seem attainable, however: a P antagonist would decrease or suppress the effects of P, when administered, for example, to the estrogen-primed, spayed rabbit, in which the endometrium responds in a characteristic fashion to P.

But effective P antagonists were difficult to identify because they often had interfering weak agonist activity or other problematic biological properties inherent to the molecule (for example, an estrogen derivative that has antiprogesterone activity still conserves its estrogenic properties; these would be "side effects" of the antiprogestin). Furthermore, it was expensive and time-consuming to perform the necessary biological tests in vivo.

These considerations contributed to the limited enthusiasm for antiprogesterone. Djerassi, in his forecast "Birth control after 1984" (*4*), did not refer specifically to P antagonists, but he did define "As an important example of future contraceptive methodology. . . 'a once-a-month' pill with luteolytic or abortifacient properties, or both. . .[i]deally, the agent might be active any time during the first 8 weeks after fertilization." Discovery of the uterine PR, the main molecular target for an antiprogestin in mammals, changed the situation considerably (*5*). Soluble preparations of the PR provided a simple and economical way to detect a potential P antagonist, since, according to the simplest hypothesis, an antiprogesterone should bind to the receptor competitively, but unlike an agonist, should not trigger the hormonal response.

Competitive binding studies with radiolabeled P or other proges-

INSERM U 33 (Communications hormonales) and Faculté de Médecine, Université Paris-Sud, Lab-Hormones, 94275 Bicêtre, France.

tins became the most powerful tool for the screening of candidate antiprogesterone molecules (*6*). When a compound was found to compete for binding to the receptor, it could be subsequently tested for its antagonistic activity against administered or endogenous P in animal models.

Affinity and structure. There is no known parameter of ligand binding that can predict differential agonistic or antagonistic activity of a steroid. The earlier belief that the rapid dissociation of ligand from the receptor could help in selecting antihormonal compounds (*7*) was erroneous because weak agonists were not distinguished from antagonists. In fact, in the chick oviduct system (*8*), 4-hydroxytamoxifen, a pure antiestrogen (with no agonistic effect), has an affinity for the estrogen receptor that is higher than that of the physiological agonist estradiol (*9*). This result encouraged the search for high-affinity derivatives. However, even though tamoxifen, the most commonly used antiestrogen, has low affinity for the receptor, it is highly effective, largely because of its low metabolic clearance rate and hence sustained concentration in the blood (*10*). Thus, affinity is not necessarily a fundamental criteria in assessing the efficacy of antihormonal compounds.

Tamoxifen and other nonsteroidal antiestrogens have a triphenylethylene structure, with two rings, α and δ, which correspond to the A and D rings of hormonal steroids, as in the nonsteroidal estrogen diethylstilbestrol (Fig. 2) (*11*). The third phenyl group of tamoxifen occupies a position near carbon-11 on the β-side of the overall steroid plane, a spatial organization that is of great importance in antihormonal function.

During the 1970s, the synthesis of 11β-substituted steroids became relatively easy through the use of the "11β-epoxidation pathway" (*12*). Several compounds showed high affinity for steroid receptors. The results prompted the decision, at the pharmaceutical company Roussel-Uclaf, to look for antiglucocorticosteroid derivatives. Each compound was assayed for its capacity to bind to several steroid hormone receptors, including the PR. RU 486 (11β-(4-dimethyl-amino phenyl)-17β-hydroxy-17α-(prop-1-ynyl)-estra-4,9-dien-3-one) (Fig. 2) was found to have a high affinity for both the rabbit PR and the rat glucocorticosteroid receptor (GR) (*13*). This observation did not come as a surprise since binding data already indicated some homology between the PR and GR, a concept now confirmed by molecular genetics (*14*), and since P was known to have weak antiglucocorticosteroid activity (*15*).

RU 486 analogs (*16*). RU 486 has strong antiprogesterone and antiglucocorticosteroid activities. It is a 19-norsteroid, lacking the C19-methyl group of natural P and glucocorticosteroids; similar 11β-substituted steroids could not be synthesized in the C19-methyl series. Short aliphatic 11β-substitution on 19-norsteroids (for example, vinyl) give agonistic compounds. Analogs with a 3- or 2-dimethylamino phenyl group have less antiprogesterone activity than RU 486, but a 4-acetyl-1-phenyl analog of RU 486, ZK 114057 (*17*), is highly potent. C18-substituted steroids (Org 31167 and Org 31343) (*18*) have low affinity for the PR and GR, but have specific antiprogesterone activity after oral administration (perhaps due to an unknown metabolite). C13α-methyl analogs, such as ZK 98299 (*17*), are difficult to synthesize because the configuration of the D ring is inversed in relation to natural steroids, but they are as active as regular C13β-methyl steroids.

C1, C10, and C12 substitutions, which chemically or sterically resemble the 11β group of RU 486, do not produce active analogs. A 17β-hydroxyl group and a short alkyl 17α-chain have been used for orally active synthetic 19-norprogestagens (see norethindrone in Fig. 2), replacing the natural 17β-CO-CH_3, 17α-H structure of progesterone. The 17α-propynyl side chain confers pure glucocorticosteroid activity (devoid of mineralocorticosteroid activity) (*19*), and this side chain may explain, in part, the lack of binding of RU 486 to the mineralocorticosteroid receptor.

Taken together, these results suggest that the ligand binding domain in the PR, the GR, and the androgen receptor (RU 486 is a weak antiandrogen) may include two pockets capable of accommodating relatively large hydrophobic substituents in the 11β- and 17α-positions in addition to the hydrophobic site for the steroid framework (*16*). In a few species, including the hamster (*20*), chicken (*21*), and Tammar wallaby (*22*), RU 486 does not bind to the PR (*23*). However, chick GR binds RU 486 well (*21*). Thus, in spite of modern steroid chemistry, the use of the molecular energy minimization program SCRIPT (*24*), sophisticated x-ray crystallography (*25*), and nuclear magnetic resonance studies of steroids cannot predict with certainty the binding of a steroid analog to receptors. The secondary and tertiary structures of the hormone binding site is not known, and in fact it may change upon ligand binding (for example, by an induced fit mechanism).

It is even more difficult to predict steroid activity than steroid binding. Steroid hormone–receptor complexes recognize specific hormone response elements (HREs) of the DNA, usually situated in or near the promoter region of regulated genes (*26*). This step is fundamental to the mechanism of steroid hormone action, but is more complex than was initially thought. Different receptors may interact with the same HRE, even though the sequences of different HREs for a given hormone may differ slightly, and conversely, HREs of different hormones can be very similar. Hormone-receptor complexes also affect the function of other transcription factors, and this may depend on receptor-induced changes of chromatin structure (*27*) (Fig. 3). The concept that the binding of a given ligand

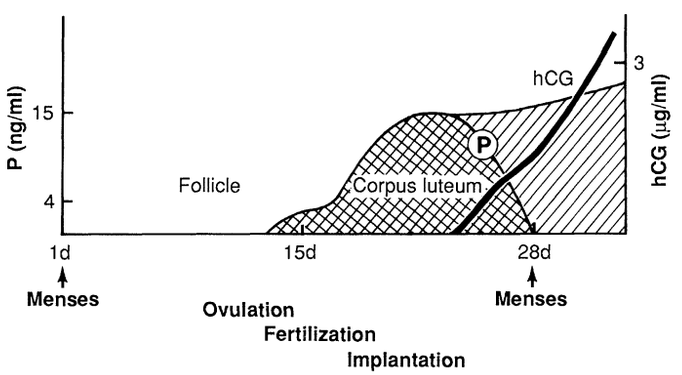

Fig. 1. Plasma concentrations of progesterone (P) (light line) during nonfertile (cross-hatched) and fertile (diagonal lines) cycles, and of hCG (heavy line) in case of fertilization and implantation; d, day.

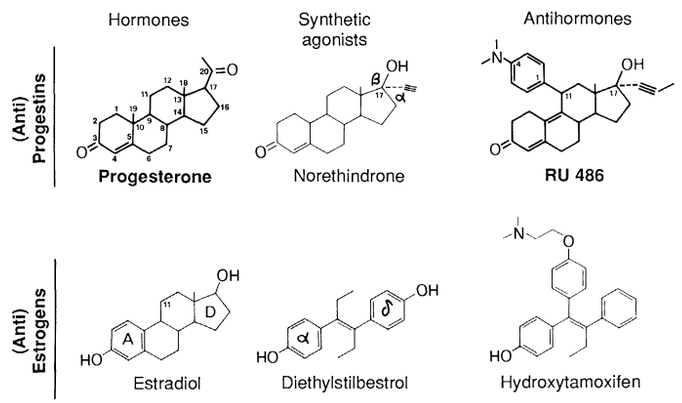

Fig. 2. Hormones, synthetic agonists, and antihormones acting on receptors. The original number of RU 486 is RU 38486 and mifepristone is its generic name.

will bring about change in receptor structure, and thus subsequent activity, is basic and probably correct, but knowledge in this field remains limited.

In short, the achievements in RU 486 research are attributable to the recognition that the receptor is the most specific and most accessible target for intervention in hormone action.

Parameters of hormone and antihormone action. The high affinity of RU 486 for the PR and GR is of the same order of magnitude as that of very active synthetic agonists, which have higher affinity for their receptors [dissociation constant (K_D) <1 n*M*] than do the corresponding natural hormones. In mammals, a typical antiprogesterone effect (shedding of the P-stimulated endometrium) is obtained with smaller quantities of RU 486 than are required for an antiglucocorticosteroid effect (for example, plasma adrenocorticotropic hormone and cortisol concentrations, which increase as a result of blockade of the negative feedback in the hypothalamus-pituitary system), even if the in vivo affinity of RU 486 for the GR may be similar to that of RU 486 for PR. It is impossible to predict the occurrence and magnitude of hormonal responses uniquely on the basis of the concentration and affinity of the ligand. Among other factors to be considered are the cellular concentration of receptors in responsive cells (*28*), the structure and number of HREs and transcription factors among the involved genes, and the nature and complexity of the observed response. For instance, it is difficult to rationally compare the dose dependency of an all-or-none, irreversible response to RU 486 (hemorrhage or endometrium shedding) with that of the gradual and reversible action on adrenocorticotropic hormone and cortisol secretion.

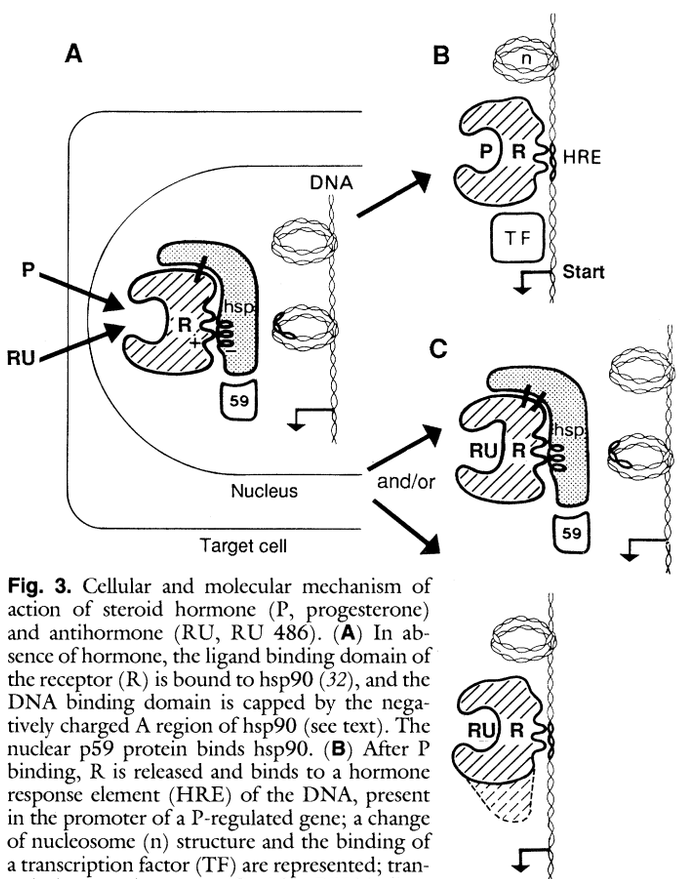

Fig. 3. Cellular and molecular mechanism of action of steroid hormone (P, progesterone) and antihormone (RU, RU 486). (**A**) In absence of hormone, the ligand binding domain of the receptor (R) is bound to hsp90 (*32*), and the DNA binding domain is capped by the negatively charged A region of hsp90 (see text). The nuclear p59 protein binds hsp90. (**B**) After P binding, R is released and binds to a hormone response element (HRE) of the DNA, present in the promoter of a P-regulated gene; a change of nucleosome (n) structure and the binding of a transcription factor (TF) are represented; transcription can then start. (**C**) After RU binding, the interaction of R to hsp90 is reinforced (*36*), and there is no interaction of R with DNA, and/or hsp is released secondarily and, although R may bind to DNA, its transformed form hinders the function of the transcription machinery (see text).

The metabolism of RU 486 is also an important parameter. Bioavailability (~70%) indicates that the absorption rate after oral administration is high. Plasma concentrations are maximal in 1 to 2 hours and reach the micromolar range after ingestion of only 25 mg. There is high-affinity binding (K_D ~1 μ*M*) to plasma orosomucoid (*13*), an α1-glycoprotein that also binds progesterone (*29*) (one site per molecule, concentration ~20 μ*M*), which appears to play an important role in the metabolism of the compound. The half-life of RU 486 in plasma is 12 to 24 hours when orosomucoid is not saturated, that is, after an intake of ≤200 mg. With a larger dose, the complex metabolic behavior is not fully understood, but a single oral administration can create high plasma concentration for several days (*30*). Metabolites are formed rapidly by mono- and di-demethylation and hydroxylation of the 17α-side chain; these metabolites have low or no affinity for the receptor and low or no antagonist activity. RU 486 and its metabolites readily cross the blood-follicle barrier of human preovulatory follicles.

Animal studies have indicated that the activity of a dose of RU 486 is comparable after oral or intravenous administration but higher after intramuscular or subcutaneous injection (after which the compound is probably released more slowly into the circulation). Vaginal administration is not efficient.

Cellular and Molecular Mechanism of Action of RU 486

RU 486, like steroid hormones themselves, enters the target cell and interacts with receptors, which are largely, if not exclusively (*31*), loosely bound in the nucleus. No metabolic activation of RU 486 in target cells has been detected.

One interpretation is that, prior to hormone binding, nuclear steroid receptors are in the 8*S* form and include the nonsteroid binding, non–DNA binding 90-kD heat shock protein (hsp90) and a nuclear protein p59 (*32*) (Fig. 3). Hsp90 binds to the ligand binding domain of receptors when the hormone is absent (*33*). Our hypothesis is that hsp90 also caps the DNA binding domain of the receptor, possibly by the α-helical "region A," which is predominantly negatively charged (*34*), and attaches to the positively charged amino acids of the second zinc finger of the DNA binding domain and of the nearby carboxyl-terminal sequence of the receptor (*14*). This mechanism would preclude the binding of the 8*S* receptor to DNA. Agonist binding would induce a conformational change of the ligand binding domain, resulting in the dissociation of hsp90, thereby allowing the binding of the receptor to DNA, specifically to the appropriate HREs. Therefore, there would be two different nuclear receptor forms: the one hetero-oligomeric and non–DNA binding, and the other capable of DNA binding (*35*).

In vitro experiments have shown that, when RU 486 binds to the PR or GR, the 8*S* receptor structure is stabilized against the transforming activity of high ionic strength or increased temperature (*36*). This is consistent with the lower binding of RU 486–PR and–GR complexes in nuclei, in contrast to that of agonist-receptor complexes (*37*). Since hsp90 binding also protects receptors from inactivation (*38*), RU 486–induced 8*S* stabilization is also consistent with the lack of receptor down-regulation observed biochemically or immunohistologically (*39*) after administration of RU 486 (*40*). Maintenance of the nontransformed, and presumably inactive, 8*S* form of the receptor can explain why in intact cells chemical methylation of the HRE of a glucocorticosteroid-induced gene occurs in the presence of RU 486 whereas the agonist dexamethasone protects HRE from methylation (*41*). Other observations are in apparent conflict with the hsp90-stabilization hypothesis as an explanation for RU 486 antihormonal activity. In vitro, RU 486–

PR and –GR complexes can bind to their corresponding HREs (*42*); however, in the experimental protocol used, the receptors are separated from hsp90, a situation that may be artificial. Complexes comprising RU 486, the transcription factor GAL4, and the GR or RU 486 and the PR inhibit the transcriptional activity of, respectively, GAL4 or a truncated PR (*43*), both of which are active regardless of the presence of hormone. These observations suggest occurrence of total or partial release of hsp90 from the receptor upon binding of RU 486 and subsequent binding of RU 486–receptor complexes to the HRE. Antihormone activity, then, would be due to the defective nature of RU 486–receptor complexes in binding to DNA or in the post–DNA binding step (for example, steric hindrance precluding the function of other transcription factors). In fact, there is no direct evidence that RU 486–receptor complexes have DNA binding activity in intact cells (*41*), and the competitive effect observed in transcription experiments (*43*) may be due to impediment of the access of transcriptionally active GAL4 or truncated receptor to DNA by the nuclear, stabilized RU 486–8*S* receptor complex. In any event, further studies should take into account the several transcription factors, phasing of nucleosomes [as demonstrated in the promoter region of the glucocorticosteroid-inducible mouse mammary tumor virus (*27*)], and the possible involvement of other, yet undefined characteristics of chromatin structure.

Presently no data contradict the hsp90-stabilizing hypothesis as presented above, but antihormone effects may be the result of several, possibly sequential, molecular mechanisms: for instance, a retarding effect on receptor activation and, secondarily, formation of defective RU 486–receptor complexes. In any case, the molecular events involved are certain to be complex, since hormone and antihormone compete for the binding site of an allosteric multimeric structure acting upon chromatin.

There is no biochemical explanation for other effects of RU 486. For example, RU 486 exhibits P-like activity in the absence of P, particularly after menopause (*44*), and it inhibits cell growth, also in the absence of agonist (*45*). Furthermore, the possible significance of the yet uncharacterized 6*S* PR form that develops in the course of RU 486 action (*46*) and the rapid dissociation of RU 486 from the receptor after separation from hsp90 (*13*) are still not understood.

Interruption of Pregnancy

It has been hypothesized, mostly on the basis of animal experiments, that a short interruption of the supply of P to the gravid human uterus would cause irreversible damage to the decidualized endometrium, leading to evacuation of the conceptus (*47*). In rats, mice, guinea pigs, rabbits, dogs, and macaque monkeys, RU 486 at doses of approximately 10 mg per kilogram of body weight per day for 1 to 4 days can interrupt early gestation (*3, 48*). When toxicological analyses were performed they indicated only the expected endocrine changes in rats and monkeys (*49*).

In women, the uterus can be evacuated safely during the first 12 weeks of pregnancy (that is, 12 weeks of amenorrhea after the first day of the last menstrual period) by vacuum aspiration. However, complications are not infrequent. Furthermore, surgical termination requires skilled doctors and nurses, and often local or general anesthesia. Consequently, RU 486 was initially used as a medical alternative in cases of voluntary pregnancy interruption.

A study (approved by the appropriate Ethics Committee) was conducted at the University Hospital in Geneva in 11 volunteers who had consented to participate and whose pregnancies were dated from 6 to 8 weeks (*50*). Nine showed signs of vaginal bleeding between 24 and 72 hours after RU 486 administration. Abortion

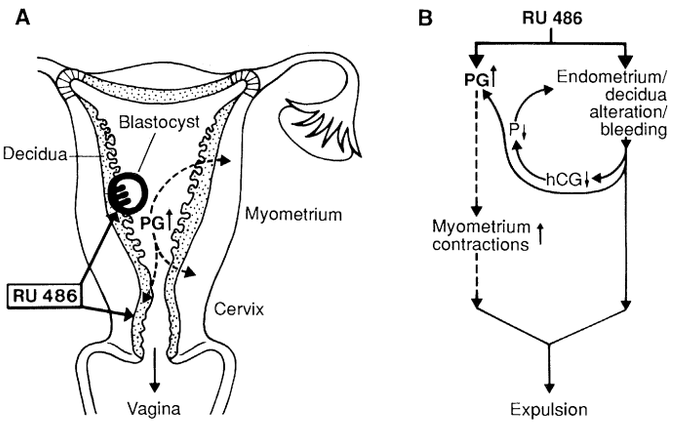

Fig. 4. Effects of RU 486 administered in early pregnancy.

was complete in 3 to 5 days in eight cases, and on day 8 in one case. Heavy bleeding necessitated instrumental intervention and transfusion in one case. In two patients, bleeding was minimal and no expulsion occurred; these were considered failures. Surprisingly, this small group of patients proved to be representative of the results of almost all subsequent studies.

After several years of trials in different countries (*51*), the simplest, most convenient and effective regimen proved to be 600 mg in a single dose (*52*). Complete expulsions were obtained in 60 to 85% of the cases while there were 1 to 10% cases of complete failure, with total absence of bleeding, and 10 to 30% of the cases resulted in incomplete expulsion. Antiprogesterone treatment primarily affects the uterine decidua: edema, necrosis, and capillary damage have been recorded, as well as decreased production of prolactin, and PAPP-A and PP12, two progesterone-regulated proteins (*53*). Levels of hCG decrease secondarily, once the chorionic tissue of the blastocyst detaches from the uterine wall, and luteolysis follows, with decreasing levels of P and estrogens, thus permitting the initiation of a new ovulatory cycle.

An increase of prostaglandins (PGs) is observed early during RU 486–induced abortion in the rat, and plasma $PGF_{2\alpha}$ increases as early as 12 to 24 hours after administration of RU 486 to pregnant women. PGs are oxytocic compounds (increasing myometrial contractions) and are produced in response to RU 486 by endometrial decidual cells; PG production also may result from a direct antiprogesterone mechanism (*54*) or may be provoked nonspecifically, when the mucosa is disrupted (Fig. 4). PGs also favor dilation and softening of the uterine cervix, which is probably also a direct effect of antiprogesterone action. PG analogs have been used medically to interrupt early pregnancy (*55*) but are considered unacceptable due to the frequency of gastrointestinal side effects such as nausea, vomiting, and diarrhea. However, small amounts of PG are very effective once P action has been interrupted, and are well tolerated (*56*). Currently, in France, where >450 centers are using RU 486 (>2000 cases per month since January 1989), a single 600-mg dose of RU 486, given orally (day 1), is followed by the administration of a small dose of a synthetic PG analog, intramuscularly or in the form of vaginal pessary, 36 to 48 hours later. The delay allows time for the reversal of transcription-dependent P activity. The procedure is highly effective (*57*), with complete success in >95% of 7-week pregnancies (and in 9-week pregnancies in trials in Great Britain), with expulsion in >60% of the cases within 4 hours after PG administration. Bleeding is induced on day 2 or 3 and continues for a mean duration of 10 days with individual variations between 4 and 40 days. This is slightly longer than after vacuum aspiration. The total measured blood loss is about 70 to 80 ml (range, 14 to 400

ml), not significantly different from what is observed with RU 486 or PG (large dose) alone, after vacuum aspiration, or during heavy menstruation (*57*). Ten percent of women require opioid analgesia. In an out patient setting, this method requires strict medical supervision in order to monitor cases of excessive blood loss [requiring dilation and curettage (D&C) in ≤1% of cases and blood transfusion in ~0.1% of RU 486–treated patients]. Also, follow-up is necessary in cases of failure that may be related to ectopic (extrauterine) pregnancies [antiprogesterone is not an acceptable treatment in these cases (*58*)]. As expected, an ovulatory cycle is restored after abortion, there are no long-term effects, and several women have successfully brought pregnancies to term.

Nevertheless, there are still 3 to 4% incomplete abortions, which require surgical intervention, and a few cases (~1%) of continued pregnancy. Under these circumstances, termination of pregnancy by aspiration or D&C is recommended, although there is to this date no evidence for a teratogenic or fetotoxic effect of RU 486 (*59*). Various studies (*60*) have not indicated specific risks for the conceptus in case of continued pregnancy. Although no adverse effects are expected in view of what is known of the mechanism of action of RU 486, caution is always prudent.

The RU 486–PG treatment may still be improved; for example, a simultaneous, oral administration of RU 486 and a PG (with retarded action) could become possible. An RU 486 analog devoid of antiglucocorticosteroid effect might also be advantageous, even though a favorable effect of the anticorticosteroid activity of RU 486 on PG metabolism has been suggested (*61*). It is noteworthy that RU 486, taken for 7 days or more at doses ≤3 mg per kilogram of body weight per day, does not result in corticosteroid insufficiency. A larger dose, such as 600 mg administered once (~10 mg/kg per day), evokes a compensatory increase of cortisol by inhibiting the negative feedback mechanism of the pituitary-adrenal system (*62*).

As currently used, the RU 486–PG medical treatment should be very useful in countries where surgical experience is limited; most women will be able to avoid instrumental intervention, with concurrent risk of infection, cervical injury, uterine perforation, and synechiae, and this treatment may also provide greater privacy.

For physical and psychological reasons, the earlier RU 486 is given for medical interruption of pregnancy, the better it is. In cases of more than 9 weeks of amenorrhea, the failure rate is likely to increase. However, RU 486 (alone) can still be medically indicated, if only for its action on the cervix: it facilitates therapeutic abortion during the course of pregnancy (*63*) and delivery of dead fetuses (*64*).

RU 486 effects on the cervix make the drug a candidate for use in certain cases of difficult delivery, especially when delivery must be induced for insufficient cervical dilation (≥10%). Studies in monkeys, however, have indicated that, although it stimulates preterm uterine activity, RU 486 does not lead to the orderly sequence of changes in PGs and cervical status observed during normal parturition (*65*). Therefore careful studies are still necessary in this area. Moreover, RU 486 crosses the fetoplacental barrier (*66*), and, in spite of lack of evidence for toxicity in the newborn, extreme caution should be taken.

Contraception

In nonpregnant women, administration of RU 486 during the last 3 to 4 days of the cycle (late luteal period) consistently precipitates the termination of a nonfertile cycle, with decreased pulse amplitude and frequency of pituitary LH secretion (*67*). The following cycle is normal (*68*). RU 486 provokes bleeding of the endometrium in spayed monkeys with an artificial estrogen-progesterone cycle (*69*) and also induces bleeding in nonpregnant women whose corpus luteum is maintained by hCG administration (*70*). Thus, it is clear that RU 486 has two main sites of action: the endometrium and the brain, where it influences LH secretion.

During the days preceding the expected menstrual period, administration of RU 486 alone gives ~80% termination rate in pregnant women, as assessed by a decrease in hCG (*71*). This observation indicates that the hormonal status of pregnancy is similar just before and just after the time the menstrual period would have been expected. RU 486 may be an effective method that has advantages over currently used steroid preparations for providing late luteal, postcoital contraception that would not involve immediate medical intervention after inopportune sexual exposure. Given an approximate 20% risk of pregnancy after unprotected sex, the postcoital use of RU 486 has an overall failure rate of 4% (20% × 20%), which is too high for the monthly use of RU 486 as a menses inducer. Thus RU 486 should be reserved for occasional, late luteal, postcoital contraception (*54*). Association of RU 486 and anti–gonadotropin-releasing hormone (GnRH) or an oral prostaglandin could possibly provide an effective once-a-month menses inducer. However, the natural variation of cycle length among women may remain a problem for the practical use of any once-a-month menses inducer.

In the middle of the luteal phase, RU 486 directly causes endometrial bleeding (*50, 67, 71, 72*). After an acute increase in the frequency and amplitude of LH pulses (*73*), there is a dose-dependent decrease of LH secretion and diminished pituitary responsiveness to GnRH (*67*). Complete luteolysis may occur, but when 2 to 3 mg of RU 486 per kilogram is given over 3 days, incomplete luteolysis is more frequently observed, with a rebound increase in LH, estradiol, and P levels; spontaneous luteolysis terminates the cycle with a second episode of uterine bleeding (*72*). Under these circumstances, it is unlikely that RU 486 has a significant, direct effect on the corpus luteum (*74*).

RU 486 given in the first half of the luteal phase inhibits glandular secretory activity and induces various vascular changes of the endometrium, suggesting that implantation may thus be prevented (*75*). Hence, one could speculate that a very small dose of RU 486 may provoke neither an LH change nor endometrial bleeding, and thus could be used for "luteal contraception," if administered for the last 10 to 12 days of the cycle, until normal menstruation occurs.

The effect of RU 486 administered in the late follicular phase suggests that preovulatory release of P may play an obligatory role in the timing and amplitude of the LH surge and may amplify the positive feedback action of estrogen on pituitary secretion of LH and follicle-stimulating hormone (*76*). After administration of the drug, maturation of the dominant follicle is delayed, and the menstrual cycle length is extended (*77*). The antiprogesterone effect of RU 486 is probably involved, but the agonist-like property of RU 486 in the virtual absence of P may also play a role. With this unresolved problem aside, these results form a basis for a possible application of RU 486 for the suppression of ovulation; in other words, RU 486 may be used as a new estrogen-free contraceptive method. This approach might be particularly desirable since, in spite of anovulation, in monkey experiments there is a residual level of 10 to 50 pg of estradiol per milliliter, which is sufficient to avoid the consequences of estrogen deprivation (*78*). Suspension of ovulation may also be involved in the promising preliminary results obtained in the treatment of endometriosis with RU 486 in monkeys and women; so-called "nonspecific antiestrogen" activity (*79*), by which RU 486 antagonizes estrogen-induced mitoses, may also play a role in this particular effect of the compound.

Finally, as a progesterone antagonist, RU 486 has also been used

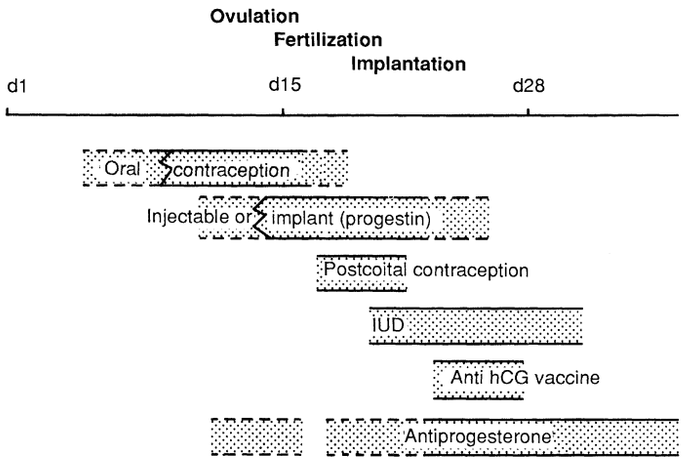

Fig. 5. Methods of fertility control. Knowledge of their mechanism tends to reduce differences between them. Efficacy is maximal at the times indicated by the solid lines; accessory effects may happen during periods indicated by dotted lines.

to treat PR-containing meningiomas (*80*) and breast cancer that has become resistant to tamoxifen (*45, 81*). This area deserves further study. It is worthwhile to note the remarkable tolerance to continuous administration of 2 to 4 mg/kg per day of RU 486 for several weeks, as observed in treatment of certain cases of hypercortisolism (*82*). The full potential of RU 486 and its analogs as antiglucocorticosteroid drugs has not yet been thoroughly researched.

"Contragestion"

Contraception is an abbreviation of contra-conception. Contemporary science has shown that "conception" cannot be thought of as only fertilization. The continuum of the reproductive process includes meiosis before fertilization, implantation (a process taking several days), and several steps necessary for the proper development of the embryo. Many methods of fertility control are not strictly "contraception" in the commonest sense of the term (Fig. 5): the intrauterine device (IUD), hormonal contraception based on progestin only, postcoital contraception, or a possible antipregnancy vaccine opposing the activity of hCG. Indeed, postfertilization interruption is an everyday process that most women have experienced at some time, even though they may not be aware of it. Therefore I propose a new word: "contragestion" (a contraction of contra-gestation), stressing the quite natural aspects of fertility and the control thereof. The debate over RU 486 may bring many women to better understand the continuous process of conception, and the drug itself may give women greater ability to exercise responsibility in matters of fertility control. We must offer people the best that science can provide so that there may be more flexibility and personal initiative in the control of familial and social problems. It is hoped that the medical community will be able to give patients in need access to a drug which, besides contragestion, seems to have other potential therapeutic utility. Scientists and physicians must communicate with the public and explain their scientific objectives as well as possible clinical advances, since "public trust is the foundation upon which biomedical reproductive research must reside" (*83*).

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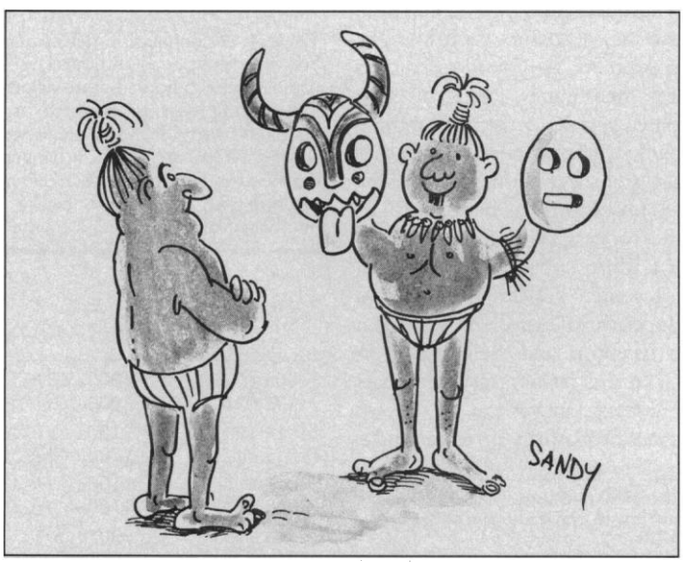

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