Review Article

Clinical applications of mifepristone in obstetrics and gynaecology

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Abstract

Roussel Uclaf in 1980 discovered Mifepristone. Mifepristone acts at the receptor level, binding strongly to the progesterone and glucocorticoid receptors, and to a lesser extent to the androgen receptors. Mifepristone is a potent antiprogesterone and antiglucocorticoid and a weak antiandrogen. Mifepristone is used for various conditions in Obstetrics and Gynaecology. Obstetrical indications include Medical abortion, second trimester abortion, cervical ripening, induction of labour. It has emerging role in emergency contraception and oestrogen-free contraception. Gynaecological indications are extended to medical management of fibroid and endometriosis. Due to antiglucocorticoid receptors present in ovarian cancer cells, Mifepristone can act as anticancer drug by virtue of its antiglucocorticoid activity. Other potential indications of Mifepristone and Gynaecology should be further developed. Here, we summarize the basic data and review related to its molecular and cellular mechanisms of action and its medical use.
Key Word: Mifepristone, Antiprogesterone, Medical abortion, Emergency contraception.

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INTRODUCTION

The discovery of mifepristone (RU486) was the achievement of a large research program on steroidal compounds with antihormone properties conducted at Roussel Uclaf in partnership with the INSERM unit of Pr. E.E. Baulieu [The quest for searching antiprogesterone, starts with Mifepristone which is the first antiprogesterone discovered. Initially it was administered for Medical abortion. Now Mifepristone is used for various conditions in Obstetrics and Gynaecology. Obstetrical indications include Medical abortion, second trimester abortion, cervical ripening, induction of labour. It has emerging role in emergency contraception and oestrogen-free contraception. Gynaecological indications are extended to medical management of fibroid and endometriosis. Due to antiglucocorticoid receptors present in ovarian cancer cells, Mifepristone can act as anticancer drug by virtue of its antiglucocorticoid activity. In this article, we explore Pharmacokinetics of Mifepristone. We capture the indications in obstetrics and Gynaecology, evaluating the safety and efficacy.

Mifepristone

The aim of reversibly suppressing hormonal activity is as old as the hormone (from the Greek word meaning to excite) concept itself. Following the demonstration of the pivotal importance of hormone receptors in hormone action and the partial elucidation of their physicochemical structure and mechanism of action, research into means of interrupting receptor function has come to the front line of the endocrinology field. (1) Antiprogestins may function as pure antagonists to the PR or as mixed agonist-antagonist molecules, also known as progesterone receptor modulators (PRMs). As compared with other more recently synthesized antiprogestins, mifepristone is predominantly an antagonist with minimal agonist activity. (2)

Steroid Structure and Metabolism

The main structural characteristic of RU486 mifepristone) is the phenyl-aminodimethyl group perpendicularly

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grafted onto the 11β-position of the steroidal skeleton. RU486 binds with high affinity to both the progesterone receptor (PR) and the glucocorticosteroid receptor (GR). There exists no pure antiprogestin compound. The antiglucocorticosteroid effect of RU486 is not useful for pregnancy termination, but conversely, this is not medically inconvenient at the usual single dose of 600 mg Nevertheless, it does limit long-term use, so efforts have been made to find new derivatives with dissociated antagonist activities Reciprocally, antiglucocorticosteroid compounds with relatively lower antiprogesterone activity than RU486 have been obtained by inversion of substituent's (1) Mifepristone acts at the receptor level, binding strongly to the progesterone and glucocorticoid receptors, and to a lesser extent to the androgen receptor. Mifipristone is potent antiprogesterone and antiglucocorticoid and a weak antiandrogen. Mifepristone, like progesterone, enters target cells and reaches its receptors; however, it interacts differently from progesterone and may produce different conformational changes in the receptor. By occupying the progesterone receptor in the nucleus, progesterone modifies the receptor's shape, enabling it to bind to chromatin, and this binding leads to gene transcription and protein synthesis. Mifepristone antagonizes these effects by occupying the receptor without stimulating gene transcription (2) Besides the binding of RU486 to steroid receptors and formation of a complex that directly modifies the response of the cellular machinery to the endogenous hormone, the distribution and metabolism of the steroid analog influences its efficiency. RU486 is readily absorbed by the oral route and the peak serum concentration occurs within 1 hr of administration. Receptors have lower affinity for demethylated and hydroxylated (in the 17α-side chain) metabolites, which are less active than RU486, but their abundance allows them to participate in the global action of the compound. (1) Nearly 80% women using Mifepristone experienced abdominal pain, uterine cramps, excessive vaginal bleeding or spooting for an average of 9-16 days. The less commo side-effects are nausea, vomiting, diarrhoea, dizziness, fatigue, fever, slight weight loss and skin rashes. The side-effects are dose and duration dependent. Pelvic inflammatory disease is a rare but serious complication. Antiglucorticoid side-effects are rarely observed in long term use with a dose of 5-100mg. Risk of endometrial carcinoma in relation to long term use of mifepristone is rare but regular transvaginal ultrasound is advisable to rule out endometrial hyperplasia.(3)

Contraindications

This product should never be prescribed in the following situations: chronic adrenal failure, known allergy to mifepristone, Severe asthma uncontrolled by corticosteroid therapy. Due to the antiglucocorticoid effect of the drug, the action of cortisol replacement may be impaired in patients with adrenal n sufficiency. In normal subjects, the pituitary and adrenals respond with increased secretion of ACTH and cortisol; this compensatory mechanism is absent in patients with adrenal failure.(2) Due to the antiglucocorticoid activity of mifepristone, the efficacy of long-term corticosteroid therapy may be decreased during the 3–4 days following mifepristone intake, and therapy should be adjusted.(2)

Drug Interactions

it is possible that ketoconazole, itraconazole, erythromycin and grapefruit juice may inhibit its metabolism and increase serum levels of mifepristone. Furthermore, rifampicin, dexamethasone and certain anticonvulsants (phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism and lower serum levels of mifepristone. (2)

Clinical Uses of Mifepristone (Ru486)

Up to now, the clinical uses of RU486 have mainly been based on its antiprogesterone activity. During the luteal phase of the non fertile cycle and during early stages of pregnancy, progesterone activity is dominant, and its interruption rapidly provokes alteration of the endometrium/decidua, which is easy to detect. The first trial, performed in Geneva in 1982 indicated the actual antiprogesterone activity of RU486 in human beings, and it was followed by many clinical studies mostly in the gynecologic and obstetrical fields. (1)

Medical Abortion

Early medical abortion with Mifepristone and Prostaglandin seems to be an effective and safe method for pregnancy termination. Mifepristone and Misopristol are now used world over for medical abortion. Initially 600 mg of Misopristone was used, followed by misopristol. Dose of Misopristol was decreased to 200mg in order to reduce the cost of medical abortion. WHO recommended Shedule for Medical Abortion is Mifepristone 200mg orally followed by 48 hours later by Misopristol 400 microgram orally on day 3. Mifepristone causes decidual breakdown by blockade of uterine progesterone receptors. As the blastocyst is implanted in uterine decidua, it leads to detachment of blastocyst, which decreases HCG production. This in turn causes a decrease in Progesterone secretion from corpus luteum, which further accentuates decdiual breakdown. Decreased endogenous progesterone, coupled with blockade of progesteronr receptors in the uterus increases uterine prostaglandin levels and sensitizes the myometrium to the contractile action of prostaglandins. It also causes

cervical softening which facilitates expulsion of the detached blastocyst. (4) Adverse events associated with mifepristone and misoprostol abortions in early pregnancy are uncommon Both Food and Drug Administration (FDA)-approved and alternative regimens have been reported to have high efficacy and few complications (5)

Ongoing Pregnancy

After more than 10 years of mifepristone use in several European countries, a few case reports of normal pregnancies and offspring have been recorded when women have taken mifepristone alone or in combination with a prostaglandin These women had not aborted and had elected to continue their pregnancies].Only one anomaly was reported after the use of mifepristone alone. This case was described as sirenomelia Although mifepristone is not a teratogenic agent, its effect on uterine contractility, when used in combination with a prostaglandin, may induce uterine retraction accounting for some of the observed defects (2)

Placental Complications in Subsequent pregnancy

Mifepristone can effectively block the binding of progesterone to the corresponding receptor in the placenta, resulting in the termination of pregnancy (Mahajan and London, 1997). The use of mifepristone as an inducer of abortion is associated with both endometrial hemorrhage and extracellular matrix (ECM) degradation. Such processes reflect reduced perivascular decidual cell hemostatic and increased ECM-degrading protease activity (Papp *et al*., 2000). Injury to the endometrium caused by mifepristone might induce the onset of the self-repair process. However, the use of mifepristone at a gestational age of 6 weeks or curettage after medical abortion might cause more serious injury to the endometrium. If the degree of injury exceeded the capacity for self-repair, there may be an irreparable long-term effect. Abruptio placenta may be one manifestation of such injury. Our data did not provide evidence that a previous Mifepristone induced abortion was itself associated with placental complications in subsequent pregnancy. However, other factors related to medical abortion—such as a gestational age weeks at abortion, a curettage after abortion and a longer interpregnancy interval—may increase the
risk of abruptio placenta.(6)

Second Trimester Abortion

Second trimesters abortions constitute 10–15% of all induced abortions worldwide but are responsible for two-thirds of major abortion-related complications the combination of mifepristone and misoprostol is now an established and highly effective method for second trimester abortion. Future studies should focus on improving pain management, the treatment of women with failed medical abortion after 24 hours, and the safety of medical abortion regimens in women with a previous caesarean section or uterine scar. For second trimester abortion (13–24 weeks of gestation), medical abortion with mifepristone followed by a PG analogue is an appropriate method and has been shown to be safe and effective, according to WHO and the RCOG. It has been well proven that pre-treatment with mifepristone 24–48 h before PG administration increases the success rate, shortens the induction-to-abortion interval and reduces the amount of PGs required in the second trimester Second trimester abortion in prior caesarean section patients should be carried out with caution.

Dose Shedule

Mifepristone 200 mg orally, followed 36– 48 hours later by misoprostol 800 micrograms vaginally and thereafter by repeated doses of 400 micrograms misoprostol orally, every 3 hours, to a maximum of 4 oral doses. The combined regimen of mifepristone and misoprostol has an abortion rate as high as 97% and the median induction-to-abortion interval is as low as 6.0 hours.31 The effect of misoprostol is dependent on the route of administration. Maximal priming effect on the myometrium is achieved 36–48 hours after pre-treatment with mifepristone. More studies are also needed to evaluate the optimal combination of mifepristone and misoprostol in women with prior caesarean section. (7)

Cervical ripening with ru486 prior to surgical abortion

Cervical maturation, as demonstrated by an increase in the cervical diameter and a decrease in cervical resistance to mechanical dilation, is favored by RU486 and includes increase of water and hyaluronic acid content and collagenase activation. In humans, data observed during first- and econd-trimester pregnancy termination and expulsion after fetal death also indicated that RU486 can induce cervical maturation. Several placebo-controlled studies were performed to evaluate the efficacy of RU486 in cervical ripening prior to vacuum aspiration. Results indicated a significant effect of RU486, with an increase in cervical diameter when the compound is given 24 h prior to measurement of the cervix. The increase in cervical diameter was linearly related to the dose, up to 400mg. The duration of the subsequent vacuum aspiration was significantly inversely related to the dose. In all cases, the mechanical resistance was reduced after RU486. In comparison with gemeprost (a 1-mg pessary) given 3–4 h prior to calibration, the increase in cervical diameter induced by RU486 was the same or greater. However, abdominal pain was significantly more frequent after gemeprost (43%) than after RU486 (10%). The antisteroid is better tolerated, but it has to be given 36–48

h prior to surgical procedure as compared with 3–4 h for prostaglandin. (1)

Induction of Labour

Mifepristone is potentially a method of inducing labour in late pregnancy by increasing uterine contractility and by increasing the sensitivity of the uterus to the actions of prostaglandins. In the study conducted by Rutuja Athawale , the women who were induced with mifepristone 200 mg per orally showed drastic improvement in cervical score within 24-48 hours and decreased the cesarean rate in the study group and amount of dose requirement of augmentation of labour with Misoprostol or Oxytocin, lesser NICU admission and maternal complications. Mifepristone has a potential as a method of inducing labour in late pregnancy through its actions in antagonizing progesterone, thus increasing uterine contractility and by increasing the sensitivity of the uterus to the actions of prostaglandins. Mifepristone, is known to cause softening and dilation of the human pregnant cervix and an increase in uterine activity. Mifepristone is associated with an increase in the chance of vaginal delivery within 24-48 hours with decreasing incidence of LSCS. Hence mifepristone combined with or without augmentation is a safe, efficient, economical and convenient induction agent for initiation of labor in women at term. Therefore, this may justify future trials comparing mifepristone with the routine cervical ripening agents currently in use. (8) In a primate model (the macaque), mifepristone administration induced prostaglandin F2alpha production by decidua, but not prostaglandin E2 production by amnion. In women, mifepristone combined with subsequent prostaglandins is also being commonly used for labour induction after fetal death in later pregnancy Theoretically, mifepristone has appeal as a method of inducing labour in women with previous caesarean section as it does not involve administering exogenous oxytocic drugs that have the potential to over-stimulate, and even rupture, the uterus. More work is this area may be justified. A single-dose therapy of 200 mg is likely to be the preferred dose for such trial. (9) RU486 crosses the placental barrier, and therefore, it is mandatory to evaluate the possible consequences of cortisol antagonism in the newborn. Preliminary trials for cases of postdate pregnancies or other medical indications for labor induction, , show that RU486 is able to induce labor and is well-tolerated by both newborn and mother. The number of hypoglycemic episodes up to 48 h after birth was identical in RU486- and placebo-treated groups. Other studies are in progress to determine the minimal dose of RU486 necessary to induce labor. (1)

Emergency postcoital contraception

Emergency post-coital contraception (EC) is an effective method of preventing pregnancy when used appropriately. Mifepristone has also been studied, mostly in China, as an emergency contraceptive option within 120 hours of unprotected sexual activity at much lower doses (10 to 50 mg). As with other emergency contraceptive options, the effect of mifepristone varies based on the timing of administration within the menstrual cycle. During the follicular phase, mifepristone delays the estrogen rise, LH surge, and ovulation. In addition, it suppresses endometrial development and follicle development. These effects of mifepristone ultimately lead to inhibition of ovulation. After ovulation, mifepristone inhibits endometrial development and blocks the expression of necessary endometrial receptors. The endometrium remains immature, thus preventing implantation from effectively occurring. Mifepristone is the only pill that, at higher doses (200 to 600 mg), is effective once implantation occurs and can stop an early pregnancy from continuing, thus considered an abortifacient in this context. Mifepristone should not be used in women who are breastfeeding. (10)

Early luteal-phase administration

Progesterone acts on the endometrium to prepare for implantation, and experiments in animals have shown that endometrial receptivity and embryo implantation can be modified by antiprogestins RU486 has been shown to induce epithelial cell apoptosis. Treatment with twice 200 mg of RU486 was performed on women on days 2 and 3 post-luteinizing hormone surge who had had unprotected intercourse at least once during the previous three days, one day after ovulation. Of over 157 cycles, only one pregnancy occurred. The main drawback of such an anti-implantation method is its impracticability, necessitating the detection of ovulation. In any case, larger samples are necessary in order to have a precise quantitation of the efficacy of the method.

Occasional late luteal-phase administration

In two studies , it has been demonstrated that RU486 could be used as a luteal-phase occasional contraceptive, when 400 or 600 mg are given once or twice on the day of (or the day before an) expected menses in women at risk of pregnancy. The efficacy of RU486 was the same as in early pregnancy termination (approximately 80% in women with elevated beta-h CG).(1) Latest WHO randomized trial (Hertzan *et al*) has noted that a single dose of mifepristone is as effective as LNG for EC with no difference in side-effects; periods start after 7 days-abit delayed than after LNG regimen.(11) Larger trials are under way to confirm these results, to define the optimal dose of RU486, and to evaluate its consequences on menstrual cyclicity.(1)

Co ntraceptive

Mifepristone has been referred to as a contragestational agent because it prevents pregnancy before and after conception. Mifepristone in low daily doses has contraceptive potential by inhibiting ovulation and menstruation. Because follicular development is maintained, the endometrium is exposed to oestrogen for a prolonged period unopposed by progesterone. Mifepristone as an oral contraceptive has distinct advantage over combined OC pills and progesterone only pills by having no oestrogenic side-effects and breakthrough bleeding. Mifepristone is anovel oestrogen free contraceptive when administered in low daily doses of 2to 10mg. It inhibits ovulation, menstruation and significantly suppresses effects on the endometrium. Nevertheless, unopposed oestrogen can cause hyperplastic and malignant chahges in endometrium.(3)

Monthly premenstrual (late luteal phase) administration

Giving RU486 approximately two days before the expected day of menses over several months proved unsuccessful because the failure rate (20%) renders the administration of RU486 alone unpracticable on a regular monthly basis, and also because, at the doses used, RU486 induced cycle irregularities with retardation of the next ovulation. The possibility that lower doses of RU486 combined with prostaglandin may circumvent these difficulties is currently under evaluation.

Ovulation suppression

A number of observations demonstrate that progesterone contributes to ovulation. The administration of RU486 during the follicular phase delays or suppresses ovulation, an effect that may be due to antiprogesterone action in ovaries, and to a suppressive effect of RU486 on gonadotropins. This may be obtained even with very low doses of RU486 Thus, a new method of estrogen-free contraception could be proposed. However, such a method raises the question of a prolonged estrogen activity, since, contrary to what has been reported (1) for monkeys, daily administration of RU486 (200 mg) for several months may be associated with endometrial hyperplasia It has been suggested that this problem can be avoided by using RU486 and a progestin sequentially, but the contraceptive activity of such a scheme remains to be evaluated. (1)

Endometrial contraception with daily delivery of very low dose of ru486

Continuous exposure to a very low dose of RU486 (i.e. ≥0.5 mg/day in

women may prevent implantation and possibly even fertilization without any change in ovulation and in estrogen and progesterone secretion pattern, as observed in the guinea pigs and in baboons In women, it is necessary to determine the maximal dose that does not suppress or delay ovulation but that can effect on the endometrium. Such a dose should certainly be well below 1 mg/day because this dose has been show to suppress ovulation in some women (~20%). If such a dose can be found, as preliminary data indicate and if the contraceptive effect is proved, such administration could become a very promising estrogen-free method. The action of RU486 of interfering with sperm may be involved in this effect on fertilization (1)

Male contraception

Progesterone increases calcium uptake by human sperm and favors the acrosome reaction. Recently, a negative effect on calcium uptake by RU486, as opposed to the positive effect of progesterone, has been described with human sperm. It was suggested that this effect takes place at the membrane level. Whether RU486 may be useful as a novel approach to male contraception remains an open question (1).

Treatment of fibroid

Recent studies have shown the effectiveness of various modes of medical management for the treatment of uterine leiomyomas. The most widely used medical therapy is GnRH agonists, which have antiestrogenic side effects and so cannot be used on a long term basis. Amongst the other drugs studied, anti-progesterone mifepristone is the most promising. Studies have suggested that leiomyomas growth is steroiddependent and that mitotic activity in leiomyomas is greatest in the luteal phase. Recent studies have provided further biochemical, histological and clinical evidence that progesterone has a critical role in leiomyoma growths. Sinha *et al* studied the effects of mifepristone treatment on leiomyomas, specifically on the size of the leiomyoma and decrease in associated symptoms like pain and menorrhagia. (12) Feng *et al*. demonstrate that the improvement in quality of life obtained with 2.5 or 5 mg doses of mifepristone is partially related to the reduction in symptoms, particularly pain and bleeding, but bears no relationship with reduction in uterine volume Study Conducted by Codepond reaveals that daily administration of 50 or 25 mg of RU486 for three months induced a 50% regression of uterine leiomyomatas. (13) Mifepristone can be useful in treating symptomatic women with uterine leiomyoma in the perimenopausal age group, in patients with menorrhagia awaiting surgery to improve anemia, and to reduce the size of tumors to make the surgery technically easier. Additionally this drug is cheaper than GnRH agonists. So it definitely shows promise of emerging as an alternative medical therapy for perimenopausal women and women with menorrhagia and pallor waiting for surgical intervention. Whether it can be used for all patients on a long term basis and the probability of recurrence of fibroids after

stopping the drug needs to be evaluated further with larger randomized controlled trials (12).

Treatment of endometriosis

Increasing knowledge about the pathogenesis of endometriosis at the cellular and molecular levels may give us the opportunity to use new, specific agents for treatment. The primary goal of medical treatment for endometriosis is to halt the growth and activity of endometriosis lesions. It also has a direct inhibitory effect on human endometrial cells and it can modulate the estrogen and progesterone receptor expression in both eutopic and ectopic endometrium .In addition, mifepristone is effective in decreasing the size of endometriotic implants in a primate model. Kettel *et al* published a series of studies of administration of different doses of mifepristone in women with endometriosis. A minimum dose of 50 mg mifepristone for six months demonstrated a significant regression in visible endometriotic lesions and a decrease in clinical symptoms. On the other hand, treatment of endometriosis patients with mifepristone 5 mg per day in an uncontrolled pilot study resulted in pain improvement but no change in endometriosis lesions, suggesting this dosage is too low to achieve acceptable efficacy. There is concern about the safety of long- term treatment because of the antiglucocorticoid properties of mifepristone. Hypoadrenalism must be considered as a major side effect of long-term treatment, especially with doses over 200 mg per day further large randomized clinical trials on the use of mifepristone in women with endometriosis should be performed in the future. (14)

Ovarian cancer

Studies have reported that ovarian cancer cells express glucocorticoid receptors and mifepristine can act as anticancer drug by virtue of its antiglucocorticoid activity. Mifepristone inhibits ovarian cancer cell proliferation in a dose and time dependant manner. Cytostatic effect of mifepristone has been confirmed by clonogenic survival assays. Mifepristone is effective as a single agent in-vitro and in-vivo, inhibiting the growth of human epithelial ovarian cancer cells. Repopulation of cancer cells escaping lethal chemotherapy is a critical factor hindering treatment success. One approach to inhibit tumour cell is to use cytostatic compounds between course of lethal Chemotherapy. Mifepristone by virtue of its cytostatic properties prevented the repopulation of remnant ovarian cancer cells between rounds of lethal dose cisplatin therapy. In phase II study of 44 patients of ovarian cancer refractory to cisplatin and paclitaxel, alone or in combination, mifepristone in a dose of 200mg/day has shown positive response.(3)

Other uses of ru486 as an antiprogestin agent

The usefulness of RU486 in other tumors containing PR remains to be evaluated.. Recently, the prolonged remission of a (low grade) osteolytic leiomyosarcoma, a tumor containing PR, has been observed during long-term administration of RU486 Antilymphoproliferative effects as well as antioxidant properties have recently been reported It is probably the local use of RU486, or derivatives with preponderant antiglucocorticosteroid activity will exert action. For instance, an antiglucocorticosteroid could accelerate the healing of wounds and burns, particularly in stressed or aging patients. (1) Studies in animals have suggested that antiprogestinscould be used in other tumors including meningiomas, gliomasand ovarian, prostate and endometrial cancer.

DISCUSSION

RU486 has proved to be a remarkably active antiprogesterone and antiglucocorticosteroid agent in human beings. It would be desirable to have derivatives with only one of these two antagonistic activities, but considering the similarities between receptors involved and responsive machineries in target cells, this may be difficult to obtain. Mifepristone exhibited a strong affinity to the progesterone and the glucocorticoid receptors. Consequently, it exerted competitive antagonism to these hormones both in vitro and in animal experiments. The identification of antiprogesterone activity led to the proposition of mifepristone use for the termination of early human pregnancy. Mifepristone, at a dose of 600 mg initially used alone, was then used with a subsequent low dose of prostaglandin that led to a success rate of 95% as a medical method for early TOP. The RU486-plus-prostaglandin method is ready to be used at large and is close to being as convenient as any medical method of abortion may be. Studies must rapidly discern the best conditions for its distribution in parts of the world where there are problems of accessibility, including developing countries. In parallel, other indications were extended to cervical dilatation prior to surgical TOP in the first trimester, in the therapeutic TOP for medical reasons beyond the first trimester, and for labor induction in case of fetal death in utero. More studies are necessary to define the optimal therapeutic schedule and to assess the consequences of neonatal exposure to RU486 on a large-scale basis. The usefulness of RU486 for obstetrical indications, including facilitation of difficult deliveries, has to be assessed rapidly. Gynecological trials, particularly in leiomyomata, should also be carefully continued. The very preliminary results obtained with tumors, including breast cancers; do indicate that further studies are necessary. The early use of RU486 as a contragestive as soon as a woman fears a pregnancy she does not want will help to defuse the abortion issue.

Research should now be conducted to define an efficient and convenient contraceptive method with RU486 or other antiprogestins. There is the possibility of a switch from antagonistic property to agonist activity, depending on the intervention of other signaling pathways. It would be desirable to have derivatives with only one of the two antagonistic properties (antiprogestin, antiglucocorticosteroid) Subtle modifications in the amino acid sequence such as those observed between receptor species and between PR is of orms or due to mutations, inherited or experimentally introduced, in the receptor molecules induce variations in antagonist binding and/or activity Thus, both chemical differences in the steroid and modifications of the receptor by genetic or biochemical processes can change the final response. This may be of importance for explaining different activities of a given compound, including RU486, according to the physiological status (interference by other signaling pathways) or pathological states (cancers with receptor mutations). Besides the political and philosophical hurdles that have delayed clinical research with this molecule, other potential indications either in areas of gynecology or oncology should be further developed Not only has RU486, because of its efficacy and safety, been the first active antagonist to progesterone and glucocorticoid usable in humans, it also addresses medical and social issues of primary importance.

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