Antiprogesterones, Today and Tomorrow

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Introduction

Antiprogesterone compounds can antagonise the biological action of the progesterone or inhibit the synthesis of progesterone. Of all the compounds tested so far, Mifepristone (RU486) has been found to be most effective and is now used in practice. It binds with high affinity to progesterone receptors throughout the body, blocking the action of the endogenous progesterone. It has been demonstrated that this drug in combination with a suitable prostaglandin is a safe and effective method of medical termination of early pregnancy and an alternative to vacuum aspiration. These compounds sensitise the uteus to prostaglandins and can be used for ripening the cervix prior to late first trimester as well as second trimester termination of pregnancy. They may induce labour, promote cervical dilatation and facilitate lactation. Besides, recent studies have shown that antiprogesterone compounds are very effective postcoital agents for contraception. Antiprogestogens could be useful as true contraceptives by prevention of implantation or inhibition of ovulation, but further research is necessary to study their effectiveness and dosage. They have a potential of treating hormone dependent conditions such as endometriosis, fibromyomatas, breast cancer and meningioma. As Mifepristone blocks the glucocorticoid receptors, it will have a role in the management of Cushing syndrome and adrenal tumours.

Progesterone is synthesised by the corpus luteum and the placenta and is vital for implantation of the embryo as well as continuation of pregnancy. The Progesterone receptor was first discovered in 1970 and Mifepristone (RU486) was the first progesterone receptor blocker and epostane was the first progesterone synthesis inhibitor to be discovered. In 1982 Roussel-Uclaf reported the synthesis of RU 486 (Mifepristone) a progesterone antagonist which competes with progesterone for its specific receptors. Subsequently ZX 98.734 (Liloprostone) and ZX 98.299 (onapristone) were synthesised as inhibitors of 3 Beta-hydroxysteroid dehydrogenase enzyme system which blocks the conversion of pregnenolone to progesterone as well as dehydroepiandrosterone to Androstenodione. Epostane is the most potent of these compounds and has been used in human studies. Thus antiprogestins are the most significant compounds developed to regulate hormonal fertility since the introduction of combined oral contraceptive pills.

With advances in medical research about receptors and antiprogestational agents and expertise in Chemistry, Pharmacology and Toxicology, the scientists of Roussel - Uclaf eventually synthesised Mifepristone - RU486. This "applied research" was followed by personal involvement of Prof. Baulieu (1989) in its application in various medical uses. Its effectiveness in interruption of pregnancy has created many controversies and political factors have delayed clinical research.

Science must be accessible and humane and overcome the political obstacles. More than 50 million abortions take place each year in this world in precarious conditions

and almost 150 thousand women die each year because of complications related to abortions. Prevention of unwanted pregnancy is possible only when there is awareness, accessibility and acceptability of family planning methods in every corner of the developed and developing world. Till then, safe and the effective methods of termination would minimise the morbidity and mortality related to termination and medical method should be available.

Chemistry:

Antiprogestins are characterised by substitutions of the 11 Beta and 17 Alpha positions of steroid ring system and bind strongly to both progesterone and glucocorrticoid receptors. The chemical name of mifepristone is 11 - (4-dimethylamino) phenyl - 17 - hydroxy - 17 - (1-propynyl) - (11 B, 17 B) - estra - 4, 9 - dien - 3- one. It is a derivative of Norethindrone, and the 17 Alpha substitution is responsible for promoting higher binding affinity to the receptor. The 11B substitution is responsible for increase in antiprogesterone activity. It is the nature and position of substitutions in the steroid structure which appears to be critical for the progesterone antagonistic activity. Efforts are being made to prepare compounds with minimum antiglucocorticoid activity. (Fig. I).

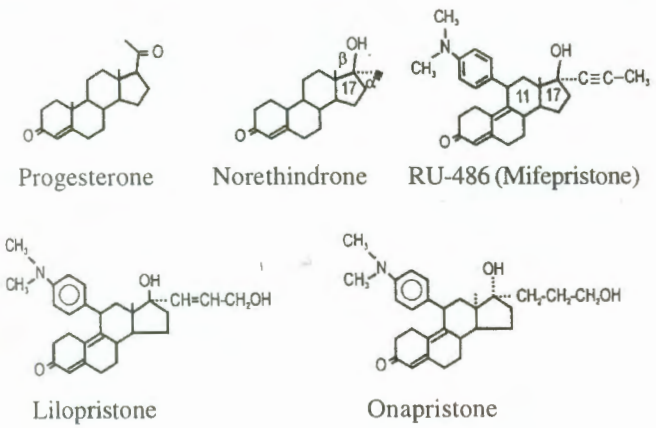

Fig 1. Structure of Progesterone and Antiprogestins.

Pharmacokinetics

The bioavailability of the drug after oral absorption is as high as 70% and the peak plasma concentration is reached within 1-2 hours. Although its half life is about 20 hours it is effective for several days and therefore it can be used as single oral dose.The drug is extensively metabolised and is excreted in bile and there is no drug accumulation in the body. Increasing doses i.e. 50, 100 and 200 mg do not lead to proportionate increase in the plasma levels and higher doses do not lead to more therapeutic effects, as unbound circulating RU486 gets rapidly metabolised.

Mechanism of action

The drug has high affinity to progesterone receptors and also binds to glucocorticoid receptors and to a lesser extent to androgen receptors. It acts on the progesterone receptors in the myometrial, endometrial and decidual cells. It is the local withdrawal of the progesterone which causes the detachment of the trophoblastic cells, resulting in impaired Beta hCG production. This converts the quiescent pregnant uterus to an active organ with spontaneous contractions and increased sensitivity to prostaglandins. Thus RU486 is effective in terminating early pregnancy when supplemented with even a small dose of prostaglandins. (Fig. II & Fig. III).

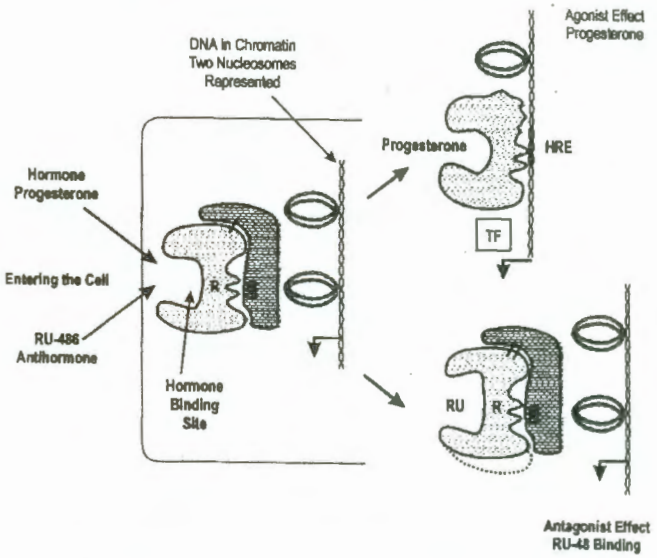

Fig II. Cellular and Molecular Mechanisms of action of Steroid Hormone & Antihormone

Progesterone maintains the endometrium and transforms it from the proliferative to secretory phase. It also facilitates the luteinizing hormone surge which initiates ovulation. As a consequence, antiprogestins may also have contraceptive potential. Although antiprogestins do delay ovulation, this effect is inconsistent unless high doses

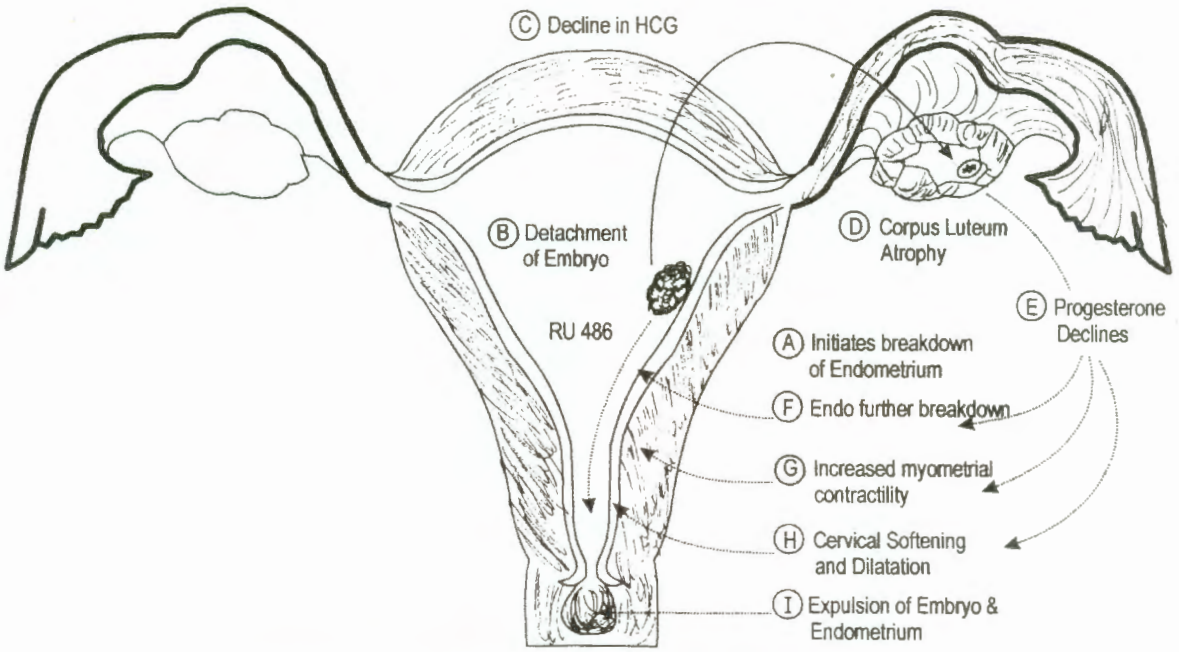

Fig III. Antiprogesterone initiates breakdown of endometrium, detachment of embryo followed by decline in HCG and then progesterone. This causes increased myometrial contractility, softening and dilatation of cervix, followed by expulsion of the embryo and endometrium

are given, whereas low doses of antiprogestins induce alteration in endometrial morphology and are therefore effective and safe postcoital agents. (Fig. IV).

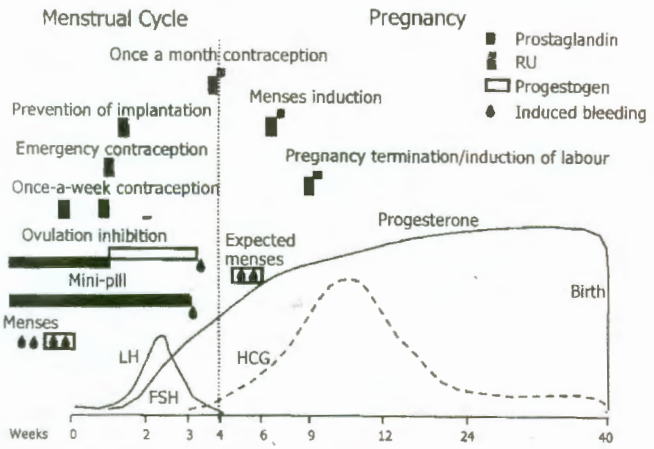

Fig IV: Effect of RU486 on different stages of Menstrual Cycle.

The role of RU486 in termination of pregnancy

Early first trimester termination

RU486 when administered alone succeeds in terminating about 75% of pregnancies but when followed by even a small dose of prostaglandins analogue, achieves complete abortion in 95-98% cases. Different analogues of PG have been used 36-48 hours after mifepristone administration for e.g. Sulprostone inj. 0.25 mg or Gemeprost (PG E1 analogue) 1mg. vaginal pessary or meteneprost (PG E2 analogue) 10 mg, or Cytotec (misoprostol) E1 analogue administered orally in dose of 400 mcg. Oral mifepristone followed by the prostaglandin analogue misoprostol is most practical and effective as both RU486 as well as misoprostol (cytotec) can be given orally and do not require refrigeration. The antiprogesterone dislodges the embryo and the prostaglandin helps to expel the products of conception. In our experience the success rate of this combination is 97% when used for cases with amenorrhoea upto 56 days and 93% when its use was extended to 63 days. The side effects of these regimens are mild nausea vomiting and abdominal cramps in less than 25% and occasional diarrhoea. The duration of bleeding is 8 - 12 days and the risk of very heavy bleeding requiring emergency curettage is about 5%. About 0.15% may need a blood transfusion. It is necessary that the patients are counselled and followed up properly and there is good medical supervision. The use of this method is an attractive alternative to suction evacuation and has the advantages

of lack of complications due to anaesthesia and surgery and maintenance of privacy.

There have been several studies where mifepristone is followed by various prostaglandin analogues for early termination of pregnancy. The success rate varies from 95% to 100% as shown in table I.

Table I

Mifepristone & PG Analogue for Early MTP

Investigator	Rx schedule	Success Rate (%) of Termination
Silvestre et al (1993)	Gemprost 1mg or Sulprostone 0.25 mg	96
Dubois et al (1988)	Gemprost 0.5mg	100
Rodger & Baird (1990)	Gemprost 0.5mg or 1mg	95
Hill et al (1990)	Gemprost 1mg	99
ICMR Task Force (1994)	9 methylene PGE2 Gel - 5 mg (Vag)	
	Sulprostone 0.25 mg	95

The orally active prostaglandin analogue - Cytotec (misoprostol) has been used by many authors in the last decade, with a success rate varying from 90-97% as shown in table II.

Table II

Success Rate of Oral Mifepristone / Misoprostol

Investigator	Success Rate (%) of Termination
Norman et al (1991)	90
Aubeny et al (1991) N = 100	95
Peyron et al (1993) N = 895	96.5
Silvestre et al (1993) N = 1298	95.4

Cervical ripening and dilatation for late first trimester abortion can be carried out by RU486. This pre-operative cervical dilatation is useful to avoid cervical trauma. Elger et al (1986) noted the significant cervical softening and dilatation by RU486 which may be responsible for production of endogenous prostaglandin by cervical stromal cells.

RU486 in 2nd trimester in MTP:

Randomised trials have shown that the use of mifepristone prior to prostaglandin leads to significant reduction in the induction to abortion interval of 2nd trimester terminations. This reduces the duration of induction abortion interval by 45 to 75 percent in various studies. Table III.

Table III

Mifepristone 200-600 MG prior to 2nd trimester abortion with Prostaglandin

Investigator	I-A Interval with only PG	I-A Interval pretreated	Reduction of I-A Interval
Reduced	(Hours)	with RU486 (Hours)	(%)
Urquhart et al (1989)	11.6	6.4	45
Rodger and Baird (1990)	11.5	6.8	57
Gotlieb & Bygdeman (1991)	13.2	6.6	50
Ho & Ma (1993)	20	4.6	75

The author has used only misoprostol vaginally in a dose of 200-400 mcg. for cases of 2nd trimester terminations or missed abortions. The time interval between the doses was varied according to the frequency and intensity of uterine contractions. The mean induction-abortion interval was 13 hours in 60 patients where this method was used and the average number of doses were four. The reduction in hospital stay was a major advantage.

Induction of labour

Chwalisz et al (1991) studied RU486 for induction of lahour in different species, including humans. It increases myometrial responsiveness to prostaglandins and oxytocin and also induces cervical ripening.

Animal studies had shown that the onset of parturition is associated with an increase in the number of gap junctions present in the myometrium. Functional coupling of myometrial cells in this way appears to be necessary to allow co-ordinated uterine contractions which are characteristic of parturition. Frydman et al (1991) and Cabrol et al (1985) have used mifepristone for induction of labour successfully. 54.5 percent of patients in Frydman's series had onset of labour compared to 18.2

per cent who received placebo. There was significant reduction in induction onset interval and the amount of oxytocin required in the treated group. There was no difference in the incidence of caesarean section. In Cabrol's study Cabrol et al(1985) 63% went in labour within 72 hours after administration of RU486. New born from mothers treated with RU486 grew faster than those of untreated mothers, as there is increase in milk output in mothers treated with RU486. Dose finding study to determine the minimum dose of RU486 necessary to induce labour are in progress. It will be necessary to establish not only its efficacy but also its safety as this drug crosses the placenta into the fetus and the pituitary-adrenal axis in the fetus may be compromised. The drug also promotes lactation perhaps due to the decline in the concentration of progesterone.

Contraceptive Potential

This antiprogesterone compound has definite potential as a contraceptive. It delays ovulation, retards endometrial maturation and reduces peak levels of placental protein 14 without affecting gonadal steroid production. The abnormalities in endometrial morphology and function are similar to those seen in infertile women with luteal phase defects. This progesterone antagonist acts at the receptor level and has been studied by Swahn, and Bygdeman (1988). The local withdrawal of progesterone influences the endometrium, hypothalamic pituitary axis and possibly the follicle and corpus luteum. The secretory transformation of the endometrium induced by progesterone is a prerequisite to enable the blastocyst to implant. This transformation is disturbed when RU486 is administered in the mid/late luteal phase. Though it is effective in preventing pregnancy, regular monthly use of antiprogestin in mid/late luteal phase will cause practical problems.

Pre-ovulatory rise in serum progesterone is related to the regulation of the mid-cycle gonadotropin surge. Immediate preovulatory administration of mifepristone has been shown to be effective in inhibiting ovulation. The existing endocrine data suggest that mifepristone disturbs the hypothalmo-pituitary ovarian axis and inhibits ovulation via its effects only on the late stages of folliculogenesis. Spitz and Bardin (1993) evaluated once-a-week administration of 10 or 50 mg. for 5 weeks on follicular development and ovulation. The ovulation was inhibited in the majority of patients. However, the return of menstruation is variable after termination of the antiprogesterone administration due to the variations in the recovery of the pituitary ovarian axis.

If RU486 is given in doses greater than 25 mg. daily in the follicular phase it suppresses oestrogen and LH surges, and ovulation remains inhibited until treatment is withdrawn. Ovulation is also inhibited with doses of 2 or 5 mg RU486 if administered daily. It is possible that a low dose regimen could be developed that would inhibit endometrial maturation and prevent implantation without disturbing ovulation and the normal rhythm of the menstrual cycle. Intermittent or daily treatment would be more practical than once-a-month treatment and prevent the possibility of failure even in a dose as low as 0.1 or 0.5 mg. Puri and Van Look (1961) studied the effects of a progesterone antagonist lilopristone (ZK 98734) on induction of menstruation, inhibition of nidation and termination of pregnancy in bonnet monkeys and showed that administration of this progesterone antagonist around the time of implantation had 100 percent pregnancy protection.

Postcoital Contraception

In the light of numerous roles played by progesterone in the regulation of mid-cycle gonadotropin secretion, endometrial maturation and early pregnancy maintenance, antiprogestins, specifically mifepristone (RU486) have been studied in recent years as possible contraceptive alternatives.

The various strategies used include ovulation inhibition, early and late luteal phase administration, and emergency contraception after unprotected intercourse. The contraceptive mechanism of action could be endocrine i.e. inhibition of ovulation and effect on endometrium. Clinical trials by Lakteenmakki et al (1988) & Couzinet et al (1986) have shown the effect of antiprogesterone on endometrial morphology and its action as an anti-implantation agent. Comparative studies of Yuzpe regimen, mifepristone (RU486), danazol and levonorgestrel have been carried out for postcoital

contraception. The effectiveness of antiprogesterone compounds is the highest and the side effects the minimal, however it is important that it is administered as early as possible after an unprotected coitus, preferably within 48 hours. Two large scale clinical studies by Glasier et al (1992) & Webb et al (1992) have shown the usefulness of mifepristone for immediate post-coital contraception compared with the Yuzpe method. The pregnancy rate was 1.5 per cent in 593 cases on Yuzpe regimen compared to nil in the mifepristone group. Besides the side effects were less compared to commonly used Yuzpe method, the incidence of nausea being 60-70% with the Yuzpe regimen, compared to 37 to 40% in the mifepristone group. Table IV.

Table IV
Comparison of two regimens for postcoital contraception

Events	Mifepristone (600 mg) (Rpt after 12 hrs)	Yuzpe Method 100mcg. EE+500mcg
No: of patients	593	593
No: of Preg.	0	9
Preg. Rate (%)	0	1.5
Side effects (%)		
None	38	13
Nausea/Vomiting	37-40	60-70
Breast symptoms	18-27	18-46
Delayed menses	39-42	6-13

Quoted from Glasier et al (1992) & Webb et al (1992).

Bhatt (1998) studied the awareness about emergency contraception in a survey of 1125 urban and 575 rural women in reproductive age group. Only 8% urban and 3% rural knew about emergency contraception. Of the 342 gynaecologists surveyed, only 30% had some knowledge about this.

He has studied 168 women, who had unprotected coitus or failed contraception between 1980 and 1995. He had given Estrogen and progesterone similar to the Yuzpe regimen within 10 days after coitus. Only 54 women presented within 72 hours and most of them were adolescent girls or unmarried. Most women wait till the date of next menstruation. About 58% of women had coitus in midcycle during the unsafe period.

The pregnancy rate after treatment given within 72 hours was 8.6%. This was 11% when the treatment was delayed and given between 6-10 days. A more effective regimen of antiprogesterone compound and greater awareness amongst the women as well as gynaecologists is very essential.

Other Applications

The potential uses of mifepristone are numerous but need further research and clinical studies. The stigma associated with this drug is due to its use for termination of pregnancy and this has slowed down the clinical investigations on this class of drugs. The anti-progestins can potentially be used in many areas of gynaecology ranging from control of endometriosis to reduction of the size of uterine leimyomata and control of breast cancer. It has significant antiglucocortocoid properties and may be an effective adjuvant for the treatment of Cushing's syndrome.

Although pelvic endometriosis and uterine leiomyomata are both common disorders in women of reproductive age, their conservative management has never been fully satisfactory and thee is a scope for newer avenues. Both these conditions are ovarian steroid dependent and have receptors for Estrogens (ER) and progesterone (PR). The therapeutic approach is to interrupt the cyclic hormone induced changes. Unfortunately, Danazol though effective has androgenic, anabolic and other side effects such as, edema and headache. The GnRH agonists though devoid of androgenic and anabolic effets have profound hypoestrogenic effect and are associated with severe hot flushes and reduction of bone mass.

Antiprogestin in treatment of Endometriosis

Since ectopic endometrial tissue contains both ER and PR, antiprogestin - RU486 was tried on six normal cyclic woman with pelvic pain due to endometriosis. 50 mg of RU486 was given daily for 3 months and laparoscopic staging of the disease was done pre and post treatment. All women became amenorrhoeic and serum estradiol (E2) Estrone (E1), Testosterone and Androstenedione as well Serum estradiol (E2) Estrone (E1), Testosterone and Androstenedione as well Serum FSH, Serum TSH, Serum Prolactin were unchanged. 24 hour mean cortisol and

ACTH concentrations were increased after RU486 treatment. There was improvement of pelvic pain in all the subjects, but endometriotic implants had resolved in only one subject and persisted in all others on follow up laparoscopy.

Some patients reported atypical flushes. Long term studies with lower doses also indicate significant decrease in pelvic pain and dysmenorrhoea and decrease in endometriotic implants by laparoscopy in 8 out of 9 subjects. Bone mineral density of Kettle et al (1991) have also noted regression of lesion in 55%.

Uterine Leiomyomata

Receptors for both Estrogens and progesterone have been identified in uterine leiomyomas and their contents are significantly greater than in the myometrium. Pituitary-ovarian down regulation by GnRH agonists is the only medical treatment available and results in about 50% regression of tumour size. An inhibitory effect of RU486 has been noted on the growth of uterine leiomyomas. RU 486 in dose of 50mg, 25mg as well as 5mg daily dose for 3 months has been studied. Seven patients in the second group also underwent uterine blood flow studies. Each subject had pelvic sonography prior to initiation of drug therapy and monthly thereafter. The bone mineral density was also assessed before and after the therapy. The leiomyoma and myometrial tissue were obtained at surgery from six RU486 treated patients and six untreated patients. On immunohistochemical analysis, the levels of ER and PR were evaluated. In the group on 50mg dose, there was a reduction in the tumour volume by 22% at 4 weeks, 39% at 8 weeks and 49% at 12 weeks, comparable to what is achieved with GnRH agonist at 6 months of treatment. A significant decrease in PR staining with unaltered ER staining was observed both in leiomyoma and myometrium. Continuous RU486 induces chronic anovulation and may disrupt HPO axis as antiprogesterone induces ovarian acyclicity. The regression of the volume of fibroid was also significant in the group on 25mg daily dose. Even at 5mg daily dose, there was reduction of 36.5 percent after the first month, 27.2 percent after the second month and 29.2 percent after the third month of treatment.

The uterine blood flow was studied in the group on 25 mg dose. There was definite increase in vascular resistance, indicating a decrease in blood flow in the uterine artery after three months of treatment. As 25 mg dose causes greater than 50 percent reduction in the volume of fibroid unaccompanied by antiglucocorticoid effect, this drug may be effective and safe alternative for management of fibroids and endometriosis. The effectiveness and safety of longer duration yet needs to be studied and a step down dose of RU 486 is proposed, where a lower dose of 5mg can serve for a long term maintenance of regression.

Breast Cancer

Antiprogestin could be a useful alternative for treating cases of locally advanced or metastatic breast cancers, when the tumours remain functional Estrogen receptor (ER's) and Progesterone receptors (PR). The endocrine treatment for breast cancer includes surgical ablation of ovaries, pharmacological doses of steroid hormones, chemical blocade of steroid hormone biosynthesis and inhibition of endogenous steroid hormone action at the tumour with synthetic antagonists such as Tamoxifen. There is considerable evidence to suggest that progesterone in the breast has a strong proliferative effect, and this stimulating effect of progesterone on the development of the mammary gland bud can be inhibited by this progesterone antagonist.

Progesterone antagonist activity has been well documented in animal models. The PR mediated mechanism helps in the treatment of established tumour with RU486. However, only few clinical trials using RU486 have been reported.

In a trial by Machina et al (1992) and Bakker et al (1990), RU486 was used as a second line of therapy after first line of treatment witth Tamoxifen. Only 6 of the 11 patients had a short term response lasting for five months and this response was associated with the presence of PR in the tumour. It is suggested that Progesterone antagonist could have a place in hormone dependent breast cancer.

Meningioma

Meningiomas are generally benign and slow growing

tumours, but can threaten brain function. Their growth is accelerated during pregnancy and most meningiomas contain PR and often little or no ER.

Administration of RU486 in a dose 200mg per day over several months would help to treat unresectable menigiomas and achieve definite improvement in some cases.Gliomas whose growth is sensitive to glucocorticosteroids may benefit from antiprogesterones with antiglucocorticoid activity.

Cushing Syndrome

The antiglucocorticoid effects of the antiprogestins is utilised for treatment of Cushings's syndrome and found to be promising. All the antiprogestins identified so far can bind to glucocorticoid receptors and exert some glucocorticoid antagonistic activities and therefore the drug can be used in diseases that involves excess adrenal production of glucocorticoid hormones. Unfortunately, there are no pure anti-glucocorticoid antiprogestins which would not display other endocrine effects.

Any long term treatment with antiprogestins or anti-glucocorticosteroids should be carefully followed up, as signs of adrenal insufficiency may also develop and much work yet remains to be done.

Summary:

This drug, therefore has application ranging from early first trimester termination, late first trimester termination as well as second trimester pregnancy termination and induction of labour. It is a contraceptive, anti-implantation agent and menses inducer. Antiprogestins may also be used in the treatment of, endometriosis, fibromyomatas, breast cancer and steroid dependent tumours. Thus a progesterone receptor antagonist would have a major impact on female reproductive health.

There have been obstacles in the development of this drug. There have been controversies, political and non-political, difficulties in registration of drug. specially in USA and hurdles to clinical research. The potential of this drug should be fully utilised and the merits and de-merits understood to modify the therapies. There is need to collect sufficient information through clinical research.

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References

1. Aubeny E, Peyron R, Turpin CL, Renault M, Targosz V, Silverstre L, JAMA, 262 (13) 1808, 1991.
2. Baulieu E E: JAMA., 262(13): 1808, 1989.
3. Bakker G H, Setyono-Han B, Portengenh; Journal of Steroid Biochemistry & Molecular Biology 37, 789, 1990.
4. Bhatt R. V. Obs. & Gynae, Today, Vol III NO. 8, 473, 1998.
5. Cabrol D, Bouvier d Yvaire M, Hermet E, Lancet 8462, 1619, 1985.
6. Chwalisz K, Hegele-Hartung C, Fritze Meier K H Endocrinology 129, 312, 1991.
7. Couzinet B, Lestrat N, Ulmann A New England J. of Medicine 315, 1565, 1986.
8. Dubois C., Ulmann, A., and Baulieu, E.E. Fertility & Sterility 50, 593, 1988.
9. Elger W., Beier S., Chwalisz K. Steroid Biochemistry 25, 835, 1986.
10. Frydmen R, Baton C, Lelaidier C Lancet 337, 488, 1991.
11. Glasier, A. Thong K J, Dewar M New England J. of Medicine 327, 1041-1992.

12. Gottlieb C., Bygdeman M. Acta Obstetricia & Gynecologica Scandinavia 70, 199, 1991.
13. Hill N. C. W., Selinger M., Fergusan J. :Br J. of Obst & Gyn 97, 487, 1990.
14. HO P. C., Ma H. K. Contraception 47, 123, 1993.
15. ICMR - Task Force on Hormonal Contraception. Contraception 49, 87-1994.
16. Kettel L M, Murphy A A, Mortola JF; Fertility & Sterility 56, 402, 1991.
17. Lakteenmakki P, Rapeli T, Kaananen M; Fertility & Sterility 50, 36, 1998.
18. Michina H, Nishino Y, Neef G; Steroid Biochemisttry & Molecular Biology 41, 339-1992.
19. Norman J.E., Thong K. J., and Baird D.T. Lancet 338, 1233, 1991.
20. Peyron R., Aubeny E., Targosz V. New England J. of Medicine 328, 1509, 1993.
21. Puri C. P. and Van Look P. F. Frontiers of Hormone Research 19, 127, 1961.
22. Rodger M. W., and Baird D. T. Br J. of Obst & Gyn 97, 41, 1990.
23. Swahn M L, Bygdeman M; Br. J. of Obst. & Gyn 95. 126: 1988.
24. Spitz, I M & Bardin C W; Contraception (In press) Clinical Applications of Mifepristone RU486 and Other Antiprogestins Editors - Molla S Donalson, Laneta Dorflinger, Sarah S Brown & Leslie Z Benet National Academy Press, Washington DC, 1993.
25. Silvestre L., Dubois C., Renault M. New England J. of Medicine 322, 645, 1993.
26. Urquhart D. R. Bahzade C., and Templeton AA. Human Reproduction 4, 202, 1989.
27. Webb, AMC, Russell J, Elstein M Br Med J 305, 927, 1992.