

Progesterone antagonists and progesterone receptor modulators: an overview

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Abstract

Since the original description of the structure of the antiprogestin, mifepristone, was published, numerous related compounds have been synthesized which may function as progesterone antagonists (PAs) or progesterone receptor modulators (PRMs). The latter are mixed agonists–antagonists. Both PAs and PRMs have therapeutic applications in female health care. Mifepristone is predominantly a PA and displays only minimum agonist activity in certain systems. Together with a prostaglandin, mifepristone can terminate pregnancies of less than 9 weeks duration, and it may also be used at later gestational ages. Mifepristone causes expulsion of the uterine contents following intrauterine fetal death. A mifepristone–prostaglandin combination has been shown to be very effective treatment in women with menses delay of 11 days or less. Many PAs and PRMs display antiproliferative effects in the endometrium. Serum estradiol levels however remain in the early to mid-follicular phase range. For this reason, they have application in the treatment of endometriosis and myoma without being associated with bone loss and hypoestrogenism. PRMs may also find application in the treatment of dysfunctional bleeding as well as an adjunct to estrogens in hormone replacement therapy in postmenopausal women. Many PAs have contraceptive potential by suppressing follicular development and blocking the LH surge. Low doses may also be potential contraceptives by retarding endometrial maturation without affecting ovulation or inducing bleeding. Mifepristone is an excellent agent for use as an emergency “postcoital” contraceptive. PAs may also be useful in IVF programs to prevent a premature LH surge and to delay the emergence of the implantation window. In addition to their use in women’s health care, mifepristone and several other PAs are potent antiglucocorticoid agents and may be used to treat ACTH-independent Cushing’s syndrome. They may also be used in the treatment of tumors containing steroid receptors and in other situations which require suppression of the ACTH–cortisol axis.

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1. Introduction

The first report on RU486 (mifepristone), a progestin and glucocorticoid receptor antagonist, was published by Philibert et al. in 1981 [1]. Since then numerous related progesterone receptor ligands have been synthesized [2] which exhibit a spectrum of activity ranging from pure progesterone antagonists (PAs) to mixed agonists/antagonists.

The actions of progesterone as well as PAs are mediated by the progesterone receptor (PR). In the target cell, progesterone produces a dramatic change in conformation of the PR that is associated with transforming (or activating) PR from a non-DNA binding form to one that will bind to DNA. This transformation is accompanied by a loss of associated heat shock proteins and dimerization. The activated PR dimer then binds to specific DNA sequences within the

promotor region of progesterone responsive genes. These are referred to as progesterone response elements (PREs). The agonist-bound PR is believed to activate transcription by associating with coactivators, which act as bridging factors between the receptor and the general transcription machinery (Fig. 1) [3,4]. This is followed by increases in the rate of transcription producing agonist effects at the cellular and tissue levels. For a detailed review, please see the contribution of Leonhardt and coworkers in this volume as well as the reviews of Leonhardt and Edwards [5] and Giangrande and McDonnell [6].

These progesterone receptor ligands exhibit a spectrum of activity ranging from pure antagonists to mixed agonists/antagonists. These latter compounds are currently known as progesterone receptor modulators (PRMs), selective progesterone receptor modulators (SPRMs), meso-progestins or partial agonist–antagonists [7–9]. Initially PAs were divided into Type 1 and Type 2 antagonists. Type 1 antagonists were regarded as “pure” PAs which

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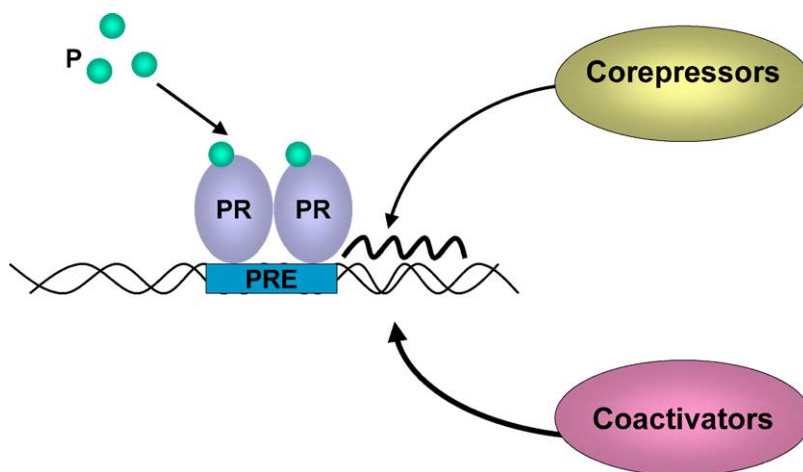


Fig. 1. In the presence of progesterone (P) or a progesterone agonist, there is loss of heat shock proteins and dimerization of the PR. The activated PR dimer binds to the progesterone-responsive elements (PREs). The agonist-bound PR then activates transcription by associating with coactivators. The effect of the corepressors is blocked.

fully antagonized PR function. An example is onapristone (ZK98299). In contrast, Type 2 antagonists (e.g. mifepristone) may stimulate PR action depending on the cell type, the promoter context and other signaling pathways. Formally it was believed that Type 1 PAs failed to bind to PREs whereas Type 2 PAs did bind [10]. Currently it is believed that Type 1 PAs do bind to PREs but promote a conformational change distinct from that induced by Type 2 PAs [11].

PAs impair the ability of receptors to interact with coactivators allowing the recruitment of corepressors (Fig. 2) such as nuclear corepressor (NCoR) and silencing mediator of retinoid and thyroid hormone (SMRT) [4,12]. Agonists on the other hand permit only a minimal interaction with corepressors (Fig. 1). It is possible that the coactivator to corepressor ratio within a given cell type determines whether a compound is an agonist, antagonist or mixed agonist–antagonist [4]. Onapristone induces a stronger association with NCoR and SMRT than mifepristone and is unable to recruit coactivator proteins [4]. For this reason, it

functions as a pure antagonist (Fig. 2). In contrast, a PRM which has both agonist and antagonist properties will recruit both coactivators and corepressors (Fig. 3). It is also possible that a PA could act via heterodimerization and competition for binding to PREs (Fig. 4).

The time-honored method to determine a compound's progestational activity is the McPhail test [9,13,14]. This assesses the degree of endometrial proliferation and transformation in immature rabbits primed initially with estradiol and then subsequently with the test substance. Antiprogestin properties may be evaluated by co-administration with progesterone. In this test, mifepristone, onapristone, ZK 230211 and CBD 2914 behave as pure PAs and demonstrate no agonist activity. In contrast, another group of compounds, the J compounds, J867, J956, and J1042 which were synthesized and characterized at Jenapharm GmbH and Co. K.G., Jena, Germany, behave as mixed agonist–antagonists. Even in large doses, J1042 is not as potent an agonist as progesterone nor as potent an antagonist as mifepristone [9].

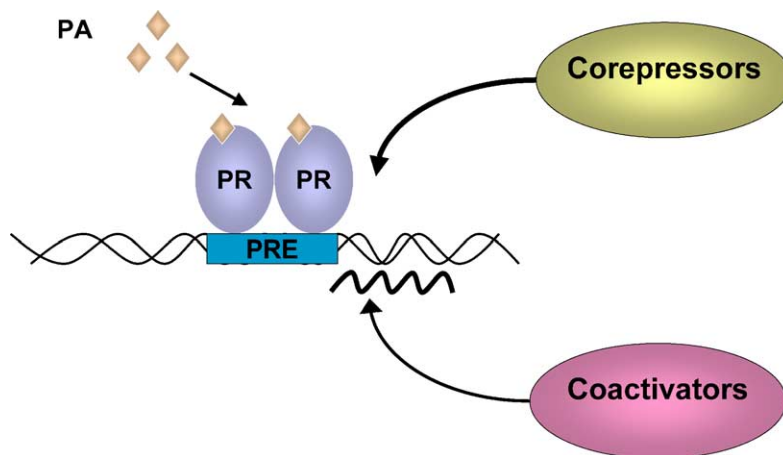


Fig. 2. With a PA the same process occurs initially as is described in Fig. 1. However, there is impaired interaction with coactivators. Corepressors are recruited in their place. This is the most likely explanation for the antagonist activity.

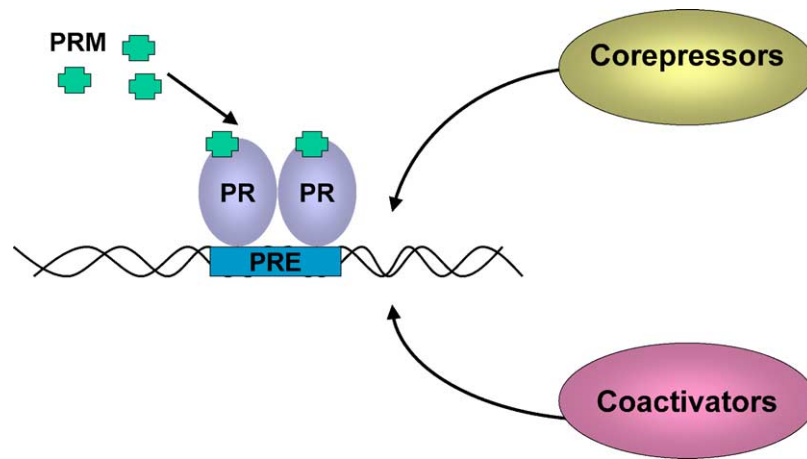


Fig. 3. With PRMs, it is likely that the ratio of recruitment of coactivator to corepressor within a given cell type determines the biological effect of the PRM and whether it is predominantly an agonist, antagonist or mixed agonist–antagonist.

These compounds thus fulfill the definition of a PRM or SPRM.

Whereas mifepristone is a pure antagonist in the McPhail test, in other model systems, it displays partial agonistic actions. In T47D cells, mifepristone converts to progesterone agonists in the presence of activators of protein kinase A (eg 8-Br-cAMP) [15–17]. It has been shown that [8] Br-cAMP potentiation of PR transcriptional activity with mifepristone is due to a loss of association with the corepressors, NCoR and SMRT, and the effect of the coactivators are predominant [3]. In contrast, an agonist effect is not seen with onapristone in view of the strong association of the PR with NCoR and SMRT [3]. T47D cells also have the ability to induce alkaline phosphatase activity in the presence of progesterone [18]. In this model, mifepristone behaves as a pure PA. On the other hand, other compounds have been synthesized which demonstrate agonist as well as mixed agonist/antagonist activities in this model [18].

Luteal regression in the guinea pig is another model to evaluate agonist and antagonist activity. PAs abolish uterine PGF-2 α secretion and luteolysis and maintain old corpora lutea. PRMs on the other hand have agonistic activity and maintain sufficient prostaglandin secretion to complete the regression of corpora lutea [9]. PRMs thus only partially suppress uterine PGF-2 α secretion in guinea pigs, which results in lower progesterone levels, compared to the normal luteal phase.

2. Clinical applications

The primary action of progesterone is to initiate and maintain pregnancy. However, progesterone has other physiological actions. By inhibiting myometrial contractility, it maintains the uterus in a quiescent state. It also facilitates the LH surge, transforms the endometrium from a proliferative

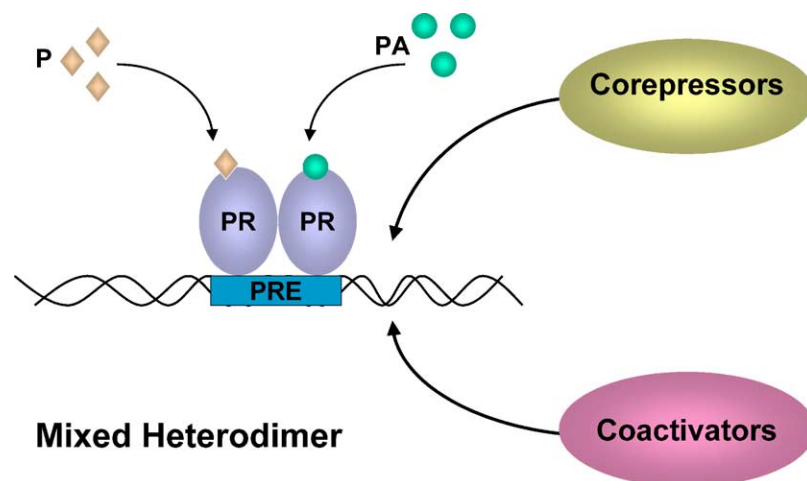


Fig. 4. This model relates to heterodimerization as another possible mechanism of action. The PA complex inhibits binding of the receptor complexed to progesterone through heterodimerization and competition for binding to PREs.

Table 1
Clinical applications^a

Short-term (usually single dose) administration of mifepristone
Medical termination of early pregnancy
Medical termination of more advanced pregnancies
Menstrual regulation
Labor induction (not recommended)
Medical management of early fetal demise
Management of fetal death
Emergency contraception
Potential use in IVF programs
Long-term administration
Uterine myoma (PRMs or PAs)
Endometriosis (PRMs or PAs)
Contraception (PAs)
Non-gynecological applications of PAs
Cushing's syndrome
Glucocorticoid antagonism (potential application in burns, glucocorticoid-dependent hypertension, arthritis, glaucoma, viral diseases possibly including AIDS)
Major depression with psychotic features
Alzheimers disease
Steroid receptor containing tumors (breast, ovary, prostate and endometrium as well as in meningiomas, gliomas and leiomyosarcomas)
GeneSwitch [®] system for ligand-dependent transgene expression

^a Mifepristone is used for all short-term indications. PRMs cannot be used because of their intrinsic agonist activity. PRMs and PAs have application in other gynecological and non-gynecological conditions.

to a secretory state and, together with estradiol, maintains endometrial integrity. PAs have the ability to antagonize all these actions. It is therefore not surprising that they have clinical application in medical termination of pregnancy, and in producing cervical softening (Table 1), applications which generally involve short-term (often single dose) administration. However, these compounds also have some long-term applications. Since mifepristone as well as some other PAs and PRMs are also potent glucocorticoid antagonists, they have several non-gynecological applications. This article concentrates on the current clinical applications of these compounds which have not been reviewed in later sections of this volume. For details of mechanism of action, antiproliferative effects on the endometrium, uses in contraception as well as emergency contraception and in Geneswitch the reader is referred to other chapters in this volume.

Because almost all the clinical studies have used the parent compound mifepristone, this is the focus of this review. Mifepristone is predominantly a PA and its main clinical application is in pregnancy termination. In contrast some of the recently developed PRMs have minimal if any abortifacient effects. This is not unexpected since by definition they possess intrinsic progesterone agonist activity. PRMs thus cannot be used for the short-term applications such as pregnancy termination. Instead they and other PAs may be used long-term in the treatment of uterine myoma and endometriosis. PAs have application in contraception as well as in other non-gynecological conditions.

2.1. Short-term administration

2.1.1. Medical termination of early pregnancy¹ with mifepristone

This medical approach to pregnancy termination has been approved in over 20 countries. Mifepristone administration is followed in 24–36 h by a prostaglandin. Although the manufacturer recommends 600 mg mifepristone, numerous studies have shown that 200 mg is equally effective [19,20]. A recent small study concluded that 100 mg mifepristone was also effective [21] although a single 50 mg dose was unable to consistently terminate pregnancy [22,23].

The synthetic PGE₁ prostaglandins currently used together with mifepristone are misoprostol and gemeprost. Misoprostol is inexpensive, can be stored at room temperature and is available in many countries for the treatment and prevention of non-steroidal drug-induced peptic ulcer. In contrast, gemeprost, a vaginal pessary, is expensive, thermolabile and requires refrigeration. Oral doses of misoprostol used range from 400 to 800 µg and the vaginal dose that has been used is 800 µg. The vaginal route is known to increase the bioavailability of mifepristone. Thus, the total dose administered with this route is likely to be greater than the oral doses tested [24]. Several studies have shown that women prefer the oral as opposed to the vaginal route of administration [25,26]. Studies have also been conducted with sublingual misoprostol. However, sublingual use is associated with more gastrointestinal adverse effects [27,28]. The success rates are similar when misoprostol is administered by the vaginal route 24, 48 and 72 h after mifepristone, although the results are not satisfactory if misoprostol is administered orally 6–8 h after mifepristone [29,30].

Although vaginal misoprostol by itself is also effective in inducing abortion, a randomized double-blind placebo-controlled study in women with gestation of 56 days or less showed that the mifepristone–misoprostol combination was significantly more effective than misoprostol alone [31].

The recommended practice is that the initial visit is conducted in the clinic where the woman is evaluated and ingests the mifepristone. She returns to the clinic after 36–48 h for the prostaglandin and remains under observation for 4–6 h. A final visit is conducted after 10–14 days to ensure that the termination was complete. Some investigators allow the woman to self-administer the prostaglandin at home [26,32]. This reduces the number of visits and consequently makes the method more acceptable. However, further clinical experience is required before this can be advocated.

When the duration of gestation was 49 days or less, the success ranged from 93.2 to 99.6%, the results being similar with both gemeprost and misoprostol [20,33,34]. After 49 days gestation, the success rate decreased when oral misoprostol was used [26,34,35]. In contrast, success remained

¹ Defined as a pregnancy with a duration of amenorrhea of 63 days or less from the date of onset of the last menstrual period.

high with gemeprost and vaginal misoprostol until 63 days, and a success of 94.3–97.5% has been reported [33,36–40]. In one study it was shown that vaginal misoprostol was associated with fewer failures than gemeprost [33]. If abortion is not imminent 4 h after vaginal misoprostol, the success rate may increase if women are given a second dose of vaginal or oral misoprostol [40].

Common causes of failure of medical termination include incomplete abortion, excess bleeding and ongoing pregnancy. When oral misoprostol is used as the prostaglandin, their incidence increases with gestational age [34,35,38]; this did not occur with gemeprost or vaginal misoprostol [36,38]. Failures are treated by surgical termination. Abdominal pain, cramps, nausea, vomiting and diarrhea are also very common side effects. On occasion, vacuum extraction may be required for other medical reasons, e.g. severe pain or vomiting [34].

Besides the duration of gestation, it has also been shown that an increase in parity is associated with a decrease in success rate. This may be related to the fact that in parous women there may be a more efficient establishment of the pregnancy at an early stage [40–42]. The abortion rate is also lower in women who have had a previous abortion (Fig. 5) [34]. There appears to be a learning curve for clinicians who perform medical termination of pregnancy. This was readily evident in a large multicenter trial conducted in the US [34]. The success was less than in other trials conducted by clinicians experienced in the method [35,36,40,43].

This method has been found to be acceptable by the majority of women, although comparative studies have shown that medical termination of pregnancy is associated with a lower complete abortion rate than surgical termination particularly in women of higher parity. However, medical termination does allow the overwhelming majority of women to avoid surgery [41].

2.1.2. Medical termination of more advanced pregnancies

Traditionally, second trimester abortion is usually performed by a surgical approach. Recently, mifepristone followed by administration of repeated doses of vaginal misoprostol at 3 h intervals has been successfully used [43,44]. In a randomized comparison study, oral misoprostol was as effective as the vaginal route [45]. Acceptable results were also obtained with mifepristone and gemeprost [43,46]. The administration of mifepristone prior to prostaglandins usually results in a reduction of the induction to abortion interval, decrease in analgesic requirement and improvement in the success rate [47]. It also allows the use of a lower dose of prostaglandins which decreases the incidence of untoward events that are associated with prostaglandin administration. Mifepristone was licensed for the termination of pregnancy of greater than 13 weeks in France and Sweden in 1992, in the UK in 1995 and in 9 other European countries in 1999 (Sitruk-Ware, personal communication).

Mifepristone followed by administration of vaginal misoprostol has also been used successfully for the termination of pregnancies of 9–13 weeks duration [48,49]. In a recent study, the administration of mifepristone (200 mg) was followed by up to five doses of misoprostol (800 µg vaginally initially and then 400 µg either vaginally or orally every 3 h) to 483 women at 64–91 days of gestation [50]. Successful medical termination was achieved in 95% of pregnancies, with efficacy declining and the ongoing pregnancy rate increasing with advancing gestational age.

2.1.3. Menstrual regulation

This is also known as endometrial (menstrual) aspiration or extraction and is usually performed surgically in women with menses delay. Mifepristone followed by gemeprost has been shown to be very effective in menstrual regulation. In one study, there was a complete abortion in 189 of 193

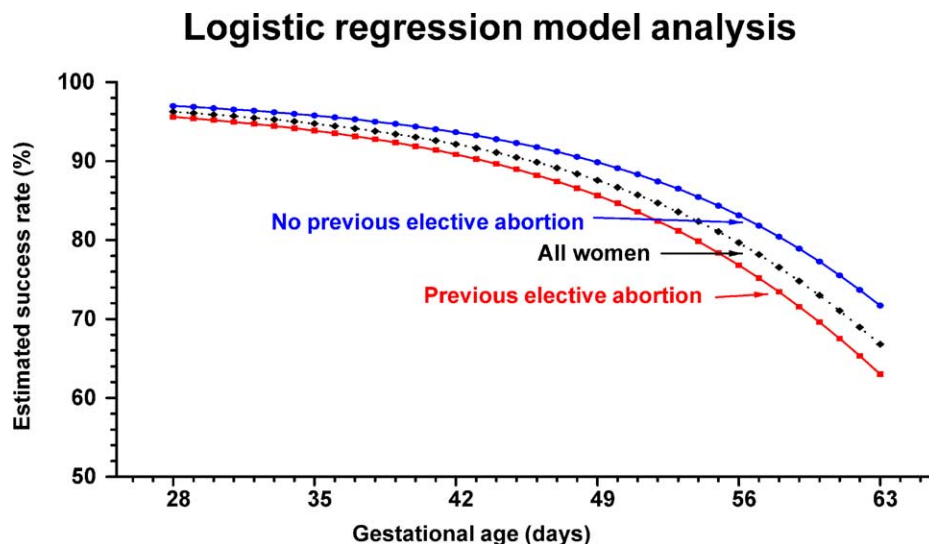


Fig. 5. Logistic regression model showing the predicted probability of success by gestational age and number of previous elective abortions. Reproduced from Spitz et al. [34], with permission.

women who presented with menses delay of 11 days or less and were shown retrospectively to be pregnant [51].

2.1.4. Labor induction

Several placebo-controlled studies have evaluated mifepristone for the induction of labor in the third trimester in women with a viable fetus [52–58]. Women receiving mifepristone were less likely to have an unfavorable cervix at 48 h and were more likely to deliver within 48 h. In some but not all of the studies, the mifepristone-treated women were less likely to undergo Caesarian section [55–58]. In one study, more women receiving mifepristone required caesarian section, but this was not statistically significant [53]. There may be effects on the fetus since mifepristone does cross the fetal placental barrier and a rise in fetal aldosterone has been reported [59]. Although not statistically significant, an increased number of uterine contractions and non-reassuring fetal heart patterns were more common with mifepristone as compared to placebo [58]. In another study, mifepristone also increased the incidence of uterine hypertonia and tachysystole. Severe fetal bradycardia after initiation of oxytocin was more common in women pretreated with mifepristone as compared to those who received prostaglandins [60]. From these results, it is apparent that the routine use of mifepristone for induction of labor cannot be recommended. Consequently the development of this indication has not been pursued by the manufacturers.

2.1.5. Medical management of early fetal demise

This encompasses missed miscarriage (presence of non-viable embryo/fetus) and blighted ovum (anembryonic pregnancy with absent embryonic echo). The majority of women are treated by surgical evacuation. A prospective randomized double-blind study showed that mifepristone alone induced expulsion in 82% of women with non-developing first trimester pregnancies, as compared to 8% in placebo-treated patients [61]. Several studies have reported the use of mifepristone either alone or more usually in combination with prostaglandin analogs in the medical management of early fetal demise. As can be seen from Table 2, the reported efficacy ranged from 74 to 93% [28,61–65] with the exception of one small study [66]. Re-

cently, it has been shown that vaginal misoprostol alone is as effective as the combination of mifepristone and vaginal misoprostol in the management of missed abortion and is associated with less bleeding (Table 2) [67].

Spontaneous incomplete abortions, presenting with bleeding and pain, are usually treated with dilatation and curettage although most can resolve without treatment [68]. A randomized trial demonstrated that 400 mg mifepristone and 400 µg misoprostol did not increase the rate of complete abortion as compared with expected management alone. A total of 82% of women randomized to mifepristone and misoprostol and 76% randomized to expectant management had an empty sac after 5 days [68].

2.1.6. Management of fetal death

Since mifepristone softens and dilates the cervix, it has the ability to induce labor following intrauterine fetal death. A dose of 200 mg two or three times a day for 2 days has been used successfully [69,70]. Another approach has been to administer misoprostol following a single dose of 200 mg mifepristone [71]. This indication is approved in 12 countries in Europe (Sitruk-Ware, personal communication). If labor has not commenced within 72 h, alternate methods should be used.

2.1.7. Potential use in IVF programs

Mifepristone may have application in superovulation induction programs since it delays the LH surge [72] and retards endometrial maturation [73]. In addition, the implantation window is “shifted” during the critical period when the endometrium is receptive to implantation [74,75]. Clearly further studies are required.

2.2. Long-term administration in non-pregnant women

2.2.1. Effects on the endometrium

In addition to the effects of PAs which are the expected consequences of progesterone antagonism, many PAs and PRMs may display antiproliferative effects in the human and non-human primate endometrium: they may suppress estrogen-dependent endometrial proliferation and mitotic activity, secretory activity and reduce endometrial thickness

Table 2
Medical management of early fetal demise with mifepristone

No. of women studied	Regimen	Efficacy (%)	Study
60	Mif 600 mg, Miso 400 µg, 200 µg, 2 h apart (O)	93	[64]
23	Mif 600 mg	82	[61]
185	Mif 200 mg. After 36–48 h, 3 sequential doses of Miso (O)	89	[63]
31	Mif 400 mg. After 36 h, Miso 400 µg (O)	52	[66]
220	Mif 200 mg. After 36–48 h, Miso 800 µg (V), 200 µg, 400 µg (V/O) at 3 h intervals	84	[65]
30	Mif 200 mg (O). After 48 h, Miso 800 µg (V)	88	[62]
56	Mif 200 mg (O). After 36–48 h, Miso 800 µg (S), 400 µg (S), 400 µg (S) at 3 h intervals	84	[28]
54	Mif 600 mg (O). After 48 h, Miso 400 µg (V) and 200 µg (V) at 2 h intervals	74	[67]
73	Miso 0.4 µg (V)	71	[67]

Mif: mifepristone; Miso: misoprostol; O: oral; V: vaginal; S: sublingual.

and wet weight [76–79]. In both women and in non-human primates, administration of PAs or PRMs is associated with a reduction of menstrual bleeding or even amenorrhea. This could be a consequence of this antiproliferative effect although it may also be due to direct effects on endometrial vasculature and may be independent of endometrial atrophy. In non-human primates and humans there is a rapid induction of amenorrhea even before any antiproliferative effects become evident [Chwalisz, personal communication]. This antiproliferative effect has been described as non-competitive [76]. It is selective and is not observed in bone or in the oviduct [78,80].

Several explanations have been given to account for these observations [7]. This may be related to the fact that the PR-A isoform inhibits estrogen receptor gene transcription induced by progestins and PAs [81]. Other potential explanations include reduced endometrial blood supply due to atrophy of spiral arteries [82,83], blockade of P-dependent growth factors such as keratinocyte growth factor [84], inhibition of angiogenesis via suppression of β fibroblast growth factor [85] or vascular endothelial growth factor [86] and cell cycle block at G2-M interphase [87]. Since mifepristone has antioxidant properties, it has been suggested that this may also possibly explain its antiproliferative effect [88]. This antiproliferative effect on the endometrium is accompanied by an increase in ER and PR [89], suggesting that the endometrial antiproliferative effect is due to progesterone antagonism. In addition to the increase in ER and PR, administration of PAs and PRMs is also associated with an increase in AR [78,90]. Since androgens suppress estrogen-induced endometrial proliferation (reviewed by Brenner et al. [90]), the increase in AR consequent to PAs could also produce these unexpected antiproliferative effects. Further evidence of the role played by androgens in this antiproliferative effect is the observation that the pure antiandrogen, flutamide, blocks the antiproliferative effects of the PAs ZK137316 and ZK230211 in the endometrium [91]. Flutamide also blocked the hyalinizing degeneration of the spiral arteries induced by PAs [91]. In view of these antiproliferative properties, both PRMs and PAs may have a role in the treatment of endometriosis and uterine myoma which are estrogen-dependent conditions [92,93].

2.2.2. Treatment of uterine myoma

A limited number of studies have been conducted with mifepristone and more recently the PRM J867. Treatment was often continued for 3–6 months and doses of mifepristone used included 5, 10, 12.5, 25, or 50 mg [94–98]. With one exception, in which a dose of 5 mg daily only produced transient effect [94,95], these doses all resulted in significant decreases in myoma volume. In another study, mifepristone (5 mg) did result in a decrease in myoma size [97]. Recently, results from the only large placebo-controlled study were presented. Doses of 5, 10 and 25 mg of the PRM J867 were administered for 12 weeks. J867 reduced myoma and uter-

ine volume as well as the intensity and duration of uterine bleeding in a dose-dependent manner [99].

2.2.3. Treatment of endometriosis

Three small clinical trials have been reported using three dose schedules of mifepristone (5 or 50 mg per day for 6 months or 100 mg per day for 3 months) [100–102]. With all schedules, there was an improvement in symptoms, and with the 50 mg dose, there was a 55% mean regression of visible endometriosis after 6 months of treatment [100–102]. The success of mifepristone in endometriosis may be related to its antiproliferative effect since endometriosis is an estrogen-dependent condition [7]. In addition it has been shown that mifepristone promotes apoptosis by overexpressing *bax*, the apoptosis-promoting gene, and down-regulating *bcl2*, the gene that protects against apoptosis. Mifepristone mediates this effect by increasing NF- κ B binding activity. This transcription factor has been identified in the promoters of *bcl2* and *bax* [103].

Unlike long-acting GnRH analogs which are generally used in the medical treatment of endometriosis and uterine myoma, mifepristone treatment was not associated with a decrease in bone mineral density [94]. This indicates that the effect of mifepristone is selective. It is antiproliferative in the endometrium but not in bone [80]. Thus, treatment with PRMs offers distinct advantages over GnRH agonists in the treatment of endometriosis and myoma [7]. It seems highly probable that some of the recently developed PRMs such as J867, which has greater progesterone agonistic activity than mifepristone and is effective in the treatment of myoma, will also be clinically efficacious in endometriosis, dysfunctional uterine bleeding and possibly, together with estrogen, in HRT.

2.2.4. Non-gynecological applications

2.2.4.1. Cushing syndrome. In high doses, mifepristone is a potent glucocorticoid antagonist and may be used in the treatment of various forms of Cushing's syndrome, such as adrenal carcinoma and ectopic ACTH secreting tumors [104,105]. Mifepristone normalizes the Cushingoid phenotype, ameliorates depression, decreases hypertension, eliminates abnormal carbohydrate metabolism and corrects glucocorticoid-induced gonadal and thyroid hormone suppression [104,105]. However, this drug cannot be used in Cushing's disease where the hypothalamic-pituitary-adrenal axis is intact but regulated at a higher set point. Under these circumstances the mifepristone-induced increase in ACTH and cortisol secretion may overcome the glucocorticoid receptor blockade [104,106]. Mifepristone however could be used to prepare a patient for surgery. Moreover, it has fewer side effects than other agents used to treat these patients. However, there is a danger of the development of hypoadrenalism, a life-threatening condition, which requires immediate treatment. Because of glucocorticoid receptor blockade, serum cortisol levels are increased

with mifepristone. Thus, if hypoadrenalism develops, the diagnosis may be difficult to confirm. Treatment should be instituted if symptoms suggest this diagnosis.

2.2.4.2. Glucocorticoid antagonism. Animal studies suggest that glucocorticoid antagonism may also be of value in the treatment of burns, glucocorticoid-dependent hypertension, arthritis, and glaucoma [106]. No clinical studies have been reported. HIV-1 encodes a 96 amino acid virion-associated accessory protein, Vpr, which functions as a transcriptional activator of several viral promoters including the HIV-1. Vpr also enhances glucocorticoid activity by functioning as a potent GR coactivator. Since AIDS patients have several manifestations of glucocorticoid excess, it is possible that Vpr may contribute to these findings. By blocking GR, mifepristone may therefore improve the clinical manifestations and course in AIDS patients [107].

Since cognition is adversely affected by high and sustained levels of glucocorticoid hormones [108] studies are currently being conducted to determine whether mifepristone can decelerate the rate of cortisol-induced cognitive decline [109,110]. The results are awaited with interest.

2.2.4.3. Major depression with psychotic features. Many patients with psychotic depression have non-suppression of cortisol following dexamethasone. In addition, they may have increased urinary cortisol and serum ACTH [111]. Five patients with major depression and psychotic features received 600 mg of mifepristone daily for 4 days in a double-blind placebo-controlled trial, and there was substantial improvement [112]. In a second study, 30 patients who met DSM-IV criteria by clinician interview were randomly assigned to receive 50, 600, or 1200 mg mifepristone once daily for 7 days. Patients receiving the 2 highest doses showed an improvement in symptomatology [111]. Mifepristone in a dose of 200 mg per day for up to 8 weeks has also been shown to have some benefit in major depression without psychotic features [113].

2.2.4.4. Steroid receptor-containing tumors. Many tumors, both benign and malignant, are steroid-dependent. Even non-steroid-dependent tumors may contain steroid receptors. For this reason, PAs may be used in the treatment of some cancers. Several small studies have been performed in breast carcinoma using both mifepristone and onapristone [114–117]. Although the results were disappointing, further studies are warranted. It is hoped that newly developed potent PAs will be more effective than mifepristone in the treatment of breast cancer. Meningiomas also contain progesterone receptors, and mifepristone has been used in the treatment of non-resectable meningiomas. Although results from early studies were encouraging, a recently completed double-blind randomized placebo-controlled study has failed to show any significant clinical benefit [118–120].

Studies in animals have suggested that PAs could be used in other tumors, including gliomas and leiomyosarcomas,

as well as in ovarian, prostate and endometrial cancer [7]. Rocereto et al. evaluated the effect of 200 mg mifepristone daily in 34 patients with refractory ovarian cancer. Three had a complete and 6 a partial response. The survival from commencement of treatment ranged from 22 to 39 months and one patient continued to respond for over 3 years [121].

3. Untoward effects

This relates almost exclusively to mifepristone since there is only very limited clinical experience with other PAs and PRMs. Because of its specific action at the progesterone and glucocorticoid receptors, serious untoward effects are rare and mifepristone is well tolerated.

3.1. In pregnant women

Adverse events reported during single dose administration for pregnancy interruption are invariably due to the prostaglandin component of the regimen and to the associated pregnancy and abortive process. Uterine rupture has been described following the administration of mifepristone and misoprostol in second or third trimester pregnancy interruption usually in women with a previous uterine scar but also on occasion in women with no previous history of cesarean section [122–124]. Although the incidence of endometritis is lower after medical than surgical abortion [34], a report of fatal clostridium toxic shock syndrome has been described following mifepristone and vaginal misoprostol [125]. The precise role if any that mifepristone played in this rare infection is unknown.

Mifepristone is not teratogenic in rats, mice, or monkeys but prostaglandins, notably misoprostol, may be associated with congenital abnormalities in the infant [126–129]. Thus, if the abortion fails, women must be informed of the possibility of congenital abnormalities in the event that pregnancy continues.

3.2. Non-pregnant women and men

Common side effects observed during long-term treatment with doses of up to 200 mg daily include fatigue, nausea, anorexia and vomiting. Weight loss, skin rashes, cessation of menses in premenopausal women, transient thinning of the hair and hot flushes have also been reported [97,118,119,130]. There is a suggestion that the incidence of hot flushes may be dose-dependent [97]. Occasional decrease in libido and gynecomastia in males have been documented, presumably due to the fact that mifepristone binds with low affinity to androgen receptors [119]. It should be noted however that mifepristone has little antiandrogenic effects in animals. Biochemical hypothyroidism has also been observed [131]. This is related to the antiglucocorticoid effect of mifepristone which inhibits iodide uptake induced by hydrocortisone and TSH [132].

On occasion, long-term mifepristone administration in doses ranging from 5 to 200 mg daily has been associated with transient elevation in hepatic enzymes [102,133–136]. Onapristone, which is closely related structurally to mifepristone, was withdrawn from clinical trials because of its effect on hepatic enzymes [114]. Low serum potassium levels have also been reported in patients with breast cancer on treatment with mifepristone, 200 mg daily, as well as in a patient with Cushing's syndrome receiving up to 2000 mg daily [105,115]. We have evaluated the long-term safety profile of mifepristone in patients with meningioma who received mifepristone in doses of 200 mg daily for up to 12 years. There were no untoward effects on serum biochemical and hematological parameters. In particular, no alterations in potassium or increases in transaminases beyond the normal range were observed (Spitz et al., in preparation).

In view of the antiglucocorticoid properties of mifepristone, hypoadrenalism must be considered as a possible consequence of long-term treatment. Although this has been reported with doses exceeding 200 mg per day, it is an uncommon occurrence in humans with an intact pituitary–adrenal axis. In one study, a severe exanthem was observed in normal males 9 days after receiving a high dose of 10 mg/kg per day [137]. This has not been observed in other studies. It is anticipated that in the low doses proposed for long-term treatment with mifepristone in conditions such as myoma, endometriosis and contraception, the incidence of untoward effects will be low.

One of the most problematic issues related to long-term treatment with PAs or PRMs is the complex effect of long-term mifepristone administration on the endometrium. In studies performed in rats and rabbits, mifepristone and other PAs may display estrogenic-like activity on the endometrium. This is related to the species and maturity of the animals [7,138–140]. These effects may also be observed in women. In a young girl with Cushing's syndrome treated with high doses of mifepristone (400 mg per day for approximately 12 months), marked endometrial enlargement was noted on MRI and ultrasound. On microscopic examination, simple endometrial hyperplasia with no evidence of atypia was observed. This endometrial enlargement resolved on cessation of mifepristone treatment [141].

In women receiving long-term high-dose mifepristone (200 mg daily) for the treatment of inoperable meningioma, there have been some isolated cases of endometrial thickening on vaginal ultrasound including a report of a woman who developed an endometrial polyp [118–120,142]. In some of these women, endometrial hyperplasia has been observed on endometrial biopsy (Spitz et al., in preparation).

The endometrial morphology in women treated with lower doses of mifepristone (50 mg daily for up to 6 months) was dyssynchronous and reminiscent of an unopposed estrogen effect. There was, however, no conclusive evidence of en-

dometrial hyperplasia [95,143]. Simple endometrial hyperplasia was observed in 28% of women receiving 5 or 10 mg mifepristone daily for 6 months [136]. Administration of 1 mg mifepristone daily for 5 months was associated with increased endometrial thickness and dilated glands in 25 and 43% of the monophasic cycles, respectively [144]. In contrast, in another study, administration of low doses of mifepristone (2 and 5 mg) daily for 4 months was associated with an inactive proliferative endometrium with cystic changes and dense stroma. There were no signs of hyperplasia or atypia [79].

The precise mechanism for these hyperplastic effects on the endometrium remains unknown. PAs and PRMs bind minimally if at all to the ER [14]. As a consequence of the lack of feedback inhibition, with the high doses of mifepristone, there is an increase in ACTH and cortisol. On occasion this is accompanied by elevation of androstenedione, estrone, testosterone and estradiol [130,131,145]. It is thus possible that endometrial aromatization of these adrenal androgens may enhance the estrogen milieu locally. However, recent studies have shown that mifepristone inhibits aromatase induction in human breast adipose tissue and blocks medroxyprogesterone acetate-induced aromatase activity in endometrial stromal cells [146,147].

Continuous administration of mifepristone in daily doses of 10 mg and below are not associated with increases in cortisol [148]. Hence the endometrial effects noted with these doses are not related to aromatization but could be a consequence of an unopposed estradiol effect on the endometrium. Progesterone levels are low because of anovulation.

One final explanation relates to the effects of the ER and PR isoforms. ER β is antiproliferative in several models [149] and often functions as a transdominant repressor of ER α transcriptional activity [150]. Since mifepristone can act as a potent ER β antagonist [151], this leaves the ER α unopposed and this could explain the estrogenic effect. Mulac-Jericevic et al. [152] have shown that selective ablation of PR-A results in a gain of progesterone-dependent proliferative activity mediated through PR-B. PR-B increases whereas PR-A diminishes estradiol responsiveness in the uterus. The precise effect on the endometrium may thus be dependent on the ratio of PR-A to PR-B.

As has already been described, in humans and non-human primates, mifepristone and other PAs or PRMs often display antiproliferative effects on the endometrium. As discussed previously, this is the rationale for their use in myoma and endometriosis. The balance between the proliferative (estrogenic) and antiproliferative (antiestrogenic) activity of these compounds on the endometrium is clearly of importance in any long-term treatment with these agents. Hopefully, with low doses of mifepristone and other PAs or PRMs any endometrial estrogen-proliferative effect will be mitigated by its antiproliferative effect. Long-term treatment with PRMs possessing agonist activity may be superior to pure PAs. The intrinsic agonist activity of a PRM may prevent endometrial proliferation.

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References

- [1] Philibert D, Deraedt R, Teutsch G. RU 38486: a potent antiglucocorticoid in vivo. In: Proceedings of the VII International Congress of Pharmacology, Tokyo, Japan; 1981.
- [2] Spitz IM, Croxatto HB, Robbins A. Antiprogestins: mechanism of action and contraceptive potential. *Annu Rev Pharmacol Toxicol* 1996;36:47–81.
- [3] Wagner BL, Norris JD, Knotts TA, Weigel NL, McDonnell DP. The nuclear corepressors NCoR and SMRT are key regulators of both ligand- and 8-bromo-cyclic AMP-dependent transcriptional activity of the human progesterone receptor. *Mol Cell Biol* 1998;18:1369–78.
- [4] Liu Z, Auboeuf D, Wong J, Chen JD, Tsai SY, Tsai MJ, et al. Coactivator/corepressor ratios modulate PR-mediated transcription by the selective receptor modulator RU486. *Proc Natl Acad Sci USA* 2002;99:7940–4.
- [5] Leonhardt SA, Edwards DP. Mechanism of action of progesterone antagonists. *Exp Biol Med (Maywood)* 2002;227:969–80.
- [6] Giangrande PH, McDonnell DP. The A and B isoforms of the human progesterone receptor: two functionally different transcription factors encoded by a single gene. *Recent Prog Horm Res* 1999;54:291–313; discussion 313–4.
- [7] Spitz IM, Chwalisz K. Progesterone receptor modulators and progesterone antagonists in women's health. *Steroids* 2000;65:807–15.
- [8] Spitz IM. Preface. *Steroids* 2000;65:543–4.
- [9] Elger W, Bartley J, Schneider B, Kaufmann G, Schubert G, Chwalisz K. Endocrine pharmacological characterization of progesterone antagonists and progesterone receptor modulators with respect to PR-agonistic and antagonistic activity. *Steroids* 2000;65:713–23.
- [10] Klein Hitpass L, Cato AC, Henderson D, Ryffel GU. Two types of antiprogestins identified by their differential action in transcriptionally active extracts from T47D cells. *Nucleic Acids Res* 1991;19:1227–34.
- [11] Gass EK, Leonhardt SA, Nordeen SK, Edwards DP. The antagonists RU486 and ZK98299 stimulate progesterone receptor binding to deoxyribonucleic acid in vitro and in vivo, but have distinct effects on receptor conformation. *Endocrinology* 1998;139:1905–19.
- [12] Onate SA, Tsai SY, Tsai MJ, O'Malley BW. Sequence and characterization of a coactivator for the steroid hormone receptor superfamily. *Science* 1995;270:1354–7.
- [13] McPhail MK. *J Physiol* 1934;83:145–56.
- [14] Philibert D. RU38486: an original multifaceted antihormone in vivo. In: Agarwal M, editor. *Adrenal steroid antagonism*. Berlin: Walter de Gruyter and Co.; 1984. p. 77–101.
- [15] Fuhrmann U, Hess Stumpp H, Cleve A, Neef G, Schwede W, Hoffmann J, et al. Synthesis and biological activity of a novel, highly potent progesterone receptor antagonist. *J Med Chem* 2000;43:5010–6.
- [16] Sartorius CA, Tung L, Takimoto GS, Horwitz KB. Antagonist-occupied human progesterone receptors bound to DNA are functionally switched to transcriptional agonists by cAMP. *J Biol Chem* 1993;268:9262–6.
- [17] Beck CA, Weigel NL, Moyer ML, Nordeen SK, Edwards DP. The progesterone antagonist RU486 acquires agonist activity upon stimulation of cAMP signaling pathways. *Proc Natl Acad Sci USA* 1993;90:4441–5.
- [18] Wagner BL, Pollio G, Leonhardt S, Wani MC, Lee DY, Imhof MO, et al. 16-Alpha-substituted analogs of the antiprogestin RU486 induce a unique conformation in the human progesterone receptor resulting in mixed agonist activity. *Proc Natl Acad Sci USA* 1996;93:8739–44.
- [19] World Health Organisation task force on postovulatory methods of fertility regulation. Termination of pregnancy with reduced doses of mifepristone. *BMJ* 1993;307:532–7.
- [20] Christin-Maitre S, Bouchard P, Spitz IM. Medical termination of pregnancy. *New Engl J Med* 2000;342:946–56.
- [21] Creinin MD, Pymar HC, Schwartz JL. Mifepristone 100 mg in abortion regimens. *Obstet Gynecol* 2001;98:434–9.
- [22] World Health Organization task force on postovulatory methods for fertility regulation. Lowering the doses of mifepristone and gemeprost for early abortion: a randomised controlled trial. *BJOG* 2001;108:738–42.
- [23] Prasad RN, Choolani M. Termination of early human pregnancy with either 50 mg or 200 mg single oral dose of mifepristone (RU486) in combination with either 0.5 mg or 1.0 mg vaginal gemeprost. *Aust NZJ Obstet Gynaecol* 1996;36:20–3.
- [24] Ziemann M, Fong SK, Benowitz NL, Banskter D, Darney PD. Absorption kinetics of misoprostol with oral or vaginal administration. *Obstet Gynecol* 1997;90:88–92.
- [25] Aubeny E, Chatellier G. A randomized comparison of mifepristone and self-administered oral or vaginal misoprostol for early abortion. *Eur J Contracept Reprod Health Care* 2000;5:171–6.
- [26] Schaff EA, Fielding SL, Westhoff C. Randomized trial of oral versus vaginal misoprostol at one day after mifepristone for early medical abortion. *Contraception* 2001;64:81–5.
- [27] Tang OS, Xu J, Cheng L, Lee SW, Ho PC. Pilot study on the use of sublingual misoprostol with mifepristone in termination of first trimester pregnancy up to 9 weeks gestation. *Hum Reprod* 2002;17:1738–40.
- [28] Wagaarachchi PT, Ashok PW, Smith NC, Templeton A. Medical management of early fetal demise using sublingual misoprostol. *BJOG* 2002;109:462–5.
- [29] Schaff EA, Fielding SL, Westhoff C, Ellertson C, Eisinger SH, Stadius LS, et al. Vaginal misoprostol administered 1, 2, or 3 days after mifepristone for early medical abortion: a randomized trial. *JAMA* 2000;284:1948–53.
- [30] Creinin MD, Schwartz JL, Pymar HC, Fink W. Efficacy of mifepristone followed on the same day by misoprostol for early termination of pregnancy: report of a randomised trial. *BJOG* 2001;108:469–73.
- [31] Jain JK, Dutton C, Harwood B, Meckstroth KR, Mishell Jr DR. A prospective randomized, double-blinded, placebo-controlled trial comparing mifepristone and vaginal misoprostol to vaginal misoprostol alone for elective termination of early pregnancy. *Hum Reprod* 2002;17:1477–82.
- [32] Schaff E, Eisinger S, Stadius L, Franks P, Gore B, Poppema S. Low-dose mifepristone 200 mg and vaginal misoprostol for abortion. *Contraception* 1999;59:1–6.
- [33] Bartley J, Brown A, Elton R, Baird DT. Double-blind randomized trial of mifepristone in combination with vaginal gemeprost or misoprostol for induction of abortion up to 63 days gestation. *Hum Reprod* 2001;16:2098–102.
- [34] Spitz IM, Bardin CW, Benton L, Robbins A. Early pregnancy termination with mifepristone and misoprostol in the United States. *N Engl J Med* 1998;338:1241–7.
- [35] Aubeny E, Peyron R, Larquier Turpin C, Renault M, Targosz V, Silvestre L, et al. Termination of early pregnancy (up to 63 days of amenorrhea) with mifepristone and increasing doses of misoprostol. *Int J Fertil* 1995;40(Suppl 2):85–91.

- [36] Ashok PW, Penney GC, Flett GM, Templeton A. An effective regimen for early medical abortion: a report of 2000 consecutive cases. *Hum Reprod* 1998;13:2962–5.
- [37] El-Rafeay H, Rajasekar D, Abdalla M, Calder L, Templeton A. Induction of abortion with mifepristone (RU486) and oral or vaginal misoprostol. *N Engl J Med* 1995;332:983–7.
- [38] Baird DT, Sukcharoen N, Thong KJ. Randomized trial of misoprostol and cervagem in combination with a reduced dose of mifepristone for induction of abortion. *Hum Reprod* 1995;10:1521–7.
- [39] Urquhart D, Templeton A, Shinwei F, Chapman M, Hawkins K, McGarry J, et al. The efficacy and tolerance of mifepristone and prostaglandin in termination of pregnancy of less than 63 days gestation, UK multicentre study: final results. *Contraception* 1997;55:1–5.
- [40] Ashok PW, Templeton A, Wagaarachchi PT, Flett GM. Factors affecting the outcome of early medical abortion: a review of 4132 consecutive cases. *BJOG* 2002;109:1281–9.
- [41] Child TJ, Thomas J, Rees M, MacKenzie IZ. A comparative study of surgical and medical procedures: 932 pregnancy terminations up to 63 days gestation. *Hum Reprod* 2001;16:67–71.
- [42] Bartley J, Tong S, Everington D, Baird DT. Parity is a major determinant of success rate in medical abortion: a retrospective analysis of 3161 consecutive cases of early medical abortion treated with reduced doses of mifepristone and vaginal gemeprost. *Contraception* 2000;62:297–303.
- [43] Bartley J, Baird DT. A randomised study of misoprostol and gemeprost in combination with mifepristone for induction of abortion in the second trimester of pregnancy. *BJOG* 2002;109:1290–4.
- [44] Ashok PW, Templeton A. Non-surgical mid-trimester termination of pregnancy: a review of 500 consecutive cases. *Br J Obstet Gynaecol* 1999;106:706–10.
- [45] Ngai SW, Tang OS, Ho PC. Randomized comparison of vaginal (200 µg every 3 h) and oral (400 µg every 3 h) misoprostol when combined with mifepristone in termination of second trimester pregnancy. *Hum Reprod* 2000;15:2205–8.
- [46] Tang OS, Thong KJ, Baird DT. Second trimester medical abortion with mifepristone and gemeprost: a review of 956 cases. *Contraception* 2001;64:29–32.
- [47] Spitz IM, Bardin CW. Clinical pharmacology of RU486: an antiprogesterin and antigluco-corticoid. *Contraception* 1993;48:403–44.
- [48] Ashok PW, Kidd A, Flett GMM, Fitzmaurice A, Graham W, Templeton A. A randomized comparison of medical abortion and surgical vacuum aspiration at 10–13 weeks gestation. *Hum Reprod* 2002;17:92–8.
- [49] Gouk EV, Lincoln K, Khair A, Haslock J, Knight J, Cruickshank DJ. Medical termination of pregnancy at 63–83 days gestation. *Br J Obstet Gynaecol* 1999;106:535–9.
- [50] Hamoda H, Ashok PW, Flett GM, Templeton A. Medical abortion at 64 to 91 days of gestation: a review of 483 consecutive cases. *Am J Obstet Gynecol* 2003;188:1315–9.
- [51] World Health Organization task force on postovulatory methods of fertility regulation. Menstrual regulation by mifepristone plus prostaglandin: results from a multicentre trial. *Hum Reprod* 1995;10:308–14.
- [52] Neilson JP, Neilson JP. Mifepristone for induction of labour (Cochrane Review). The Cochrane Library, Issue 1. Oxford: Update Software; 2003.
- [53] Elliott CL, Brennand JE, Calder AA. The effects of mifepristone on cervical ripening and labor induction in primigravidae. *Obstet Gynecol* 1998;92:804–9.
- [54] Frydman R, Lelaidier C, Baton Saint Mleux C, Fernandez H, Vial M, Bourget P. Labor induction in women at term with mifepristone (RU486): a double-blind, randomized, placebo-controlled study. *Obstet Gynecol* 1992;80:972–5.
- [55] Giacalone PL, Targosz V, Laffargue F, Boog G, Faure JM. Cervical ripening with mifepristone before labor induction: a randomized study. *Obstet Gynecol* 1998;92:487–92.
- [56] Lelaidier C, Baton C, Benifla JL, Fernandez H, Bourget P, Frydman R. Mifepristone for labour induction after previous caesarean section. *Br J Obstet Gynaecol* 1994;101:501–3.
- [57] Stenlund PM, Ekman G, Aedo AR, Bygdeman M. Induction of labor with mifepristone: a randomized, double-blind study versus placebo. *Acta Obstet Gynecol Scand* 1999;78:793–8.
- [58] Wing DA, Fassett MJ, Mishell DR. Mifepristone for preinduction cervical ripening beyond 41 weeks' gestation: a randomized controlled trial. *Obstet Gynecol* 2000;96:543–8.
- [59] Hill NC, Selinger M, Ferguson J, MacKenzie IZ. The placental transfer of mifepristone (RU486) during the second trimester and its influence upon maternal and fetal steroid concentrations. *Br J Obstet Gynaecol* 1990;97:406–11.
- [60] Giacalone PL, Daures JP, Faure JM, Boulou P, Hedon B, Laffargue F. The effects of mifepristone on uterine sensitivity to oxytocin and on fetal heart rate patterns. *Eur J Obstet Gynecol Reprod Biol* 2001;97:30–4.
- [61] Lelaidier C, Baton Saint Mleux C, Fernandez H, Bourget P, Frydman R. Mifepristone (RU486) induces embryo expulsion in first trimester non-developing pregnancies: a prospective randomized trial. *Hum Reprod* 1993;8:492–5.
- [62] Schaff EA, Fielding SL, Eisinger S, Stadalius L. Mifepristone and misoprostol for early abortion when no gestational sac is present. *Contraception* 2001;63:251–4.
- [63] Hughes J, Ryan M, Hinshaw K, Henshaw R, Rispin R, Templeton A. The costs of treating miscarriage: a comparison of medical and surgical management. *Br J Obstet Gynaecol* 1996;103:1217–21.
- [64] El-Rafeay H, Hinshaw K, Henshaw R, Smith N, Templeton A. Medical management of missed abortion and anembryonic pregnancy. *BMJ* 1992;305:1399.
- [65] Wagaarachchi PT, Ashok PW, Narvekar N, Smith NC, Templeton A. Medical management of early fetal demise using a combination of mifepristone and misoprostol. *Hum Reprod* 2001;16:1849–53.
- [66] Nielsen S, Hahlin M, Platz Christensen JJ. Unsuccessful treatment of missed abortion with a combination of an antiprogesterone and a prostaglandin E1 analogue. *Br J Obstet Gynaecol* 1997;104:1094–6.
- [67] Gronlund A, Gronlund L, Clevin L, Andersen B, Palmgren N, Lidgaard O. Management of missed abortion: comparison of medical treatment with either mifepristone + misoprostol or misoprostol alone with surgical evacuation. A multi-center trial in Copenhagen county, Denmark. *Acta Obstet Gynecol Scand* 2002;81:1060–5.
- [68] Nielsen S, Hahlin M. Expectant management of first-trimester spontaneous abortion. *Lancet* 1995;345:84–6.
- [69] Cabrol D, Bouvier D'Yvoire M, Mermet E, Cedard L, Sureau C, Baulieu EE. Induction of labour with mifepristone after intrauterine fetal death. *Lancet* 1985;2:1019.
- [70] Cabrol D, Dubois C, Cronje H, Gonnet JM, Guillot M, Maria B, et al. Induction of labor with mifepristone (RU486) in intrauterine fetal death. *Am J Obstet Gynecol* 1990;163:540–2.
- [71] Wagaarachchi PT, Ashok PW, Narvekar NN, Smith NC, Templeton A. Medical management of late intrauterine death using a combination of mifepristone and misoprostol. *BJOG* 2002;109:443–7.
- [72] Messinis IE, Krishnan M, Kazem R, Khadilkar S, Templeton AA. Effect of mifepristone on folliculogenesis in women treated with recombinant FSH. *Clin Endocrinol Oxf* 1997;46:309–14.
- [73] Sarkar NN. The potential of mifepristone (RU486) as a female contraceptive drug. *Int J Clin Pract* 2002;56:140–4.
- [74] Hegele Hartung C, Mootz U, Beier HM. Luteal control of endometrial receptivity and its modification by progesterone antagonists. *Endocrinology* 1992;131:2446–60.
- [75] Paulson RJ, Sauer MV, Lobo RA. Potential enhancement of endometrial receptivity in cycles using controlled ovarian

- hyperstimulation with antiprogestins: a hypothesis. *Fertil Steril* 1997;67:321–5.
- [76] Hodgen GD, van Uem JF, Chillik CF, Danforth DR, Wolf JP, Neulen J, et al. Non-competitive anti-oestrogenic activity of progesterone antagonists in primate models. *Hum Reprod* 1994;9(Suppl 1):77–81.
- [77] Slayden OD, Zelinski Wooten MB, Chwalisz K, Stouffer RL, Brenner RM. Chronic treatment of cycling rhesus monkeys with low doses of the antiprogestin ZK 137 316: morphometric assessment of the uterus and oviduct. *Hum Reprod* 1998;13:269–77.
- [78] Slayden OD, Brenner RM. RU486 action after estrogen priming in the endometrium and oviducts of rhesus monkeys (*Macaca mulatta*). *J Clin Endocrinol Metab* 1994;78:440–8.
- [79] Baird DT, Brown A, Critchley HO, Williams AR, Lin S, Cheng L. Effect of long-term treatment with low-dose mifepristone on the endometrium. *Hum Reprod* 2003;18:61–8.
- [80] Grow DR, Williams RF, Hsiu JG, Hodgen GD. Antiprogestin and/or gonadotropin-releasing hormone agonist for endometriosis treatment and bone maintenance: a 1-year primate study. *J Clin Endocrinol Metab* 1996;81:1933–9.
- [81] McDonnell DP, Goldman ME. RU486 exerts antiestrogenic activities through a novel progesterone receptor A form-mediated mechanism. *J Biol Chem* 1994;269:11945–9.
- [82] Zelinski Wooten MB, Slayden OD, Chwalisz K, Hess DL, Brenner RM, Stouffer RL. Chronic treatment of female rhesus monkeys with low doses of the antiprogestin ZK 137 316: establishment of a regimen that permits normal menstrual cyclicity. *Hum Reprod* 1998;13:259–67.
- [83] Chwalisz K, Brenner RM, Fuhrmann UU, Hess Stumpff H, Elger W. Antiproliferative effects of progesterone antagonists and progesterone receptor modulators on the endometrium. *Steroids* 2000;65:741–51.
- [84] Koji T, Chedid M, Rubin JS, Slayden OD, Csaky KG, Aaronson SA, et al. Progesterone-dependent expression of keratinocyte growth factor mRNA in stromal cells of the primate endometrium: keratinocyte growth factor as a progestomedin. *J Cell Biol* 1994;125:393–401.
- [85] Grow DR, Reece MT, Hsiu JG, Adams L, Newcomb PM, Williams RF, et al. Chronic antiprogestin therapy produces a stable atrophic endometrium with decreased fibroblast growth factor: a 1-year primate study on contraception and amenorrhea. *Fertil Steril* 1998;69:936–43.
- [86] Greb RR, Heikinheimo O, Williams RF, Hodgen GD, Goodman AL. Vascular endothelial growth factor in primate endometrium is regulated by oestrogen-receptor and progesterone-receptor ligands in vivo. *Hum Reprod* 1997;12:1280–92.
- [87] Heikinheimo O, Hsiu JG, Gordon K, Kim S, Williams RF, Gibbons WE, et al. Endometrial effects of RU486 in primates: antiproliferative action despite signs of estrogen action and increased cyclin-B expression. *J Steroid Biochem Mol Biol* 1996;59:179–90.
- [88] Parthasarathy S, Morales AJ, Murphy AA. Antioxidant: a new role for RU486 and related compounds. *J Clin Invest* 1994;94:1990–5.
- [89] Neulen J, Williams RF, Breckwoldt M, Chwalisz K, Baulieu EE, Hodgen GD. Non-competitive anti-oestrogenic actions of progesterone antagonists in primate endometrium: enhancement of oestrogen and progesterone receptors with blockade of postreceptor proliferative mechanisms. *Hum Reprod* 1996;11:1533–7.
- [90] Brenner RM, Slayden OD, Critchley HO. Anti-proliferative effects of progesterone antagonists in the primate endometrium: a potential role for the androgen receptor. *Reproduction* 2002;124:167–72.
- [91] Slayden OD, Brenner RM. Flutamide counteracts the antiproliferative effects of antiprogestins in the primate endometrium. *J Clin Endocrinol Metab* 2003;88:946–9.
- [92] Englund K, Blanck A, Gustavsson I, Lundkvist U, Sjoblom P, Norgren A, et al. Sex steroid receptors in human myometrium and fibroids: changes during the menstrual cycle and gonadotropin-releasing hormone treatment. *J Clin Endocrinol Metab* 1998;83:4092–6.
- [93] Brandon DD, Bethea CL, Strawn EY, Novy MJ, Burry KA, Harrington MS, et al. Progesterone receptor messenger ribonucleic acid and protein are overexpressed in human uterine leiomyomas. *Am J Obstet Gynecol* 1993;169:78–85.
- [94] Yen SSC. Use of antiprogestins in the management of endometriosis and leiomyoma. In: Donaldson MS, Dorflinger L, Brown SS, Benet LZ, editors. *Clinical applications of mifepristone (RU496) and other antiprogestins*. Washington, DC: National Academy Press; 1993. p. 189–209.
- [95] Murphy AA, Castellano PZ. RU486: pharmacology and potential use in the treatment of endometriosis and leiomyomata uteri. *Curr Opin Obstet Gynecol* 1994;6:269–78.
- [96] Yang Y, Zheng S, Li K. Treatment of uterine leiomyoma by two different doses of mifepristone. *Chin J Obstet Gynecol* 1996;31:624–6.
- [97] Eisinger SH, Meldrum S, Fiscella K, le Roux HD, Guzick DS. Low-dose mifepristone for uterine leiomyomata. *Obstet Gynecol* 2003;101:243–50.
- [98] Zeng C, Gu M, Huang H. A clinical control study on the treatment of uterine leiomyoma with gonadotrophin releasing hormone agonist or mifepristone. *Zhonghua Fu Chan Ke Za Zhi* 1998;33:490–2.
- [99] Chwalisz K, Parker L, Williamson S. Treatment of uterine leiomyomas with the novel selective progesterone receptor modulator (SPRM). *J Soc Gynecol Investig* 2003;10:301A.
- [100] Kettel LM, Murphy AA, Morales AJ, Rivier J, Vale W, Yen SS. Rapid regression of uterine leiomyomas in response to daily administration of gonadotropin-releasing hormone antagonist. *Fertil Steril* 1993;60:642–6.
- [101] Kettel LM, Murphy AA, Morales AJ, Ulmann A, Baulieu EE, Yen SS. Treatment of endometriosis with the antiprogestone mifepristone (RU486). *Fertil Steril* 1996;65:23–8.
- [102] Kettel LM, Murphy AA, Morales AJ, Yen SS. Preliminary report on the treatment of endometriosis with low-dose mifepristone (RU486). *Am J Obstet Gynecol* 1998;178:1151–6.
- [103] Han S, Sidell N. RU486-induced growth inhibition of human endometrial cells involves the nuclear factor-kappa B signaling pathway. *J Clin Endocrinol Metab* 2003;88:713–9.
- [104] Nieman LK, Chrousos GP, Kellner C, Spitz IM, Nisula BC, Cutler GB, et al. Successful treatment of Cushing's syndrome with the glucocorticoid antagonist RU486. *J Clin Endocrinol Metab* 1985;61:536–40.
- [105] Chu JW, Matthias DF, Belanoff J, Schatzberg A, Hoffman AR, Feldman D. Successful long-term treatment of refractory Cushing's disease with high-dose mifepristone (RU486). *J Clin Endocrinol Metab* 2001;86:3568–73.
- [106] Spitz IM, Bardin CW. Mifepristone (RU486): a modulator of progestin and glucocorticoid action. *N Engl J Med* 1993;329:404–12.
- [107] Mirani M, Elenkov I, Volpi S, Hiroi N, Chrousos GP, Kino T. HIV-1 protein Vpr suppresses IL-12 production from human monocytes by enhancing glucocorticoid action: potential implications of Vpr coactivator activity for the innate and cellular immunity deficits observed in HIV-1 infection. *J Immunol* 2002;169:6361–8.
- [108] McEwen BS, Davis PG, Parsons B, Pfaff DW. The brain as a target for steroid hormone action. *Annu Rev Neurosci* 1979;2:65–112.
- [109] Pomara N, Doraiswamy PM, Tun H, Ferris S. Mifepristone (RU486) for Alzheimer's disease. *Neurology* 2002;58:1436.
- [110] Belanoff JK, Jurik J, Schatzberg LD, DeBattista C, Schatzberg AF. Slowing the progression of cognitive decline in Alzheimer's disease using mifepristone. *J Mol Neurosci* 2002;19:201–6.
- [111] Belanoff JK, Rothschild AJ, Cassidy F, DeBattista C, Baulieu EE, Schold C, et al. An open label trial of C-1073 (mifepristone) for psychotic major depression. *Biol Psychiatr* 2002;52:386–92.
- [112] Belanoff JK, Flores BH, Kalezhan M, Sund B, Schatzberg AF. Rapid reversal of psychotic depression using mifepristone. *J Clin Psychopharmacol* 2001;21:516–21.

- [113] Pearson Murphy BE. Antigluco-corticoid therapies in major depression: a review. *Psychoneuroendocrinology* 1997;22(Suppl 1):S125–32.
- [114] Klijn JG, Setyono Han B, Foekens JA. Progesterone antagonists and progesterone receptor modulators in the treatment of breast cancer. *Steroids* 2000;65:825–30.
- [115] Romieu G, Maudelonde T, Ulmann A, Pujol H, Grenier J, Cavalie G, et al. The antiprogesterone RU486 in advanced breast cancer: preliminary clinical trial. *Bull Cancer* 1987;74:455–61.
- [116] Perrault D, Eisenhauer EA, Pritchard KI, Panasci L, Norris B, Vandenberg T, et al. Phase II study of the progesterone antagonist mifepristone in patients with untreated metastatic breast carcinoma: a National Cancer Institute of Canada Clinical Trials Group Study. *J Clin Oncol* 1996;14:2709–12.
- [117] Bakker GH, Setyono Han B, Portengen H, De Jong FH, Foekens JA, Klijn JG. Treatment of breast cancer with different antiprogesterone: preclinical and clinical studies. *J Steroid Biochem Mol Biol* 1990;37:789–94.
- [118] Grunberg SM, Weiss MH, Spitz IM, Ahamadi J, Sadun A, Russell CA, et al. Treatment of unresectable meningiomas with the antiprogesterone agent mifepristone. *J Neurosurg* 1991;74:861–4.
- [119] Grunberg SM. Role of antiprogesterone therapy for meningiomas. *Hum Reprod* 1994;9(Suppl 1):202–7.
- [120] Grunberg SM, Rankin C, Townsend J, Ahamadi J, Feun L, Fredricks R, et al. Phase III double-blind randomized placebo-controlled study of mifepristone (RU) for the treatment of unresectable meningioma. San Francisco, CA. *Am Soc Clin Oncol* 2001;20.
- [121] Rocereto TF, Saul HM, Aikins Jr JA, Paulson J. Phase II study of mifepristone (RU486) in refractory ovarian cancer. *Gynecol Oncol* 2000;77:429–32.
- [122] UK Multicenter Study Group. Oral mifepristone 600 mg and vaginal gemeprost for mid-trimester induction of abortion. An open multicenter study. *Contraception* 1997;56:361–6.
- [123] Phillips K, Berry C, Mathers AM. Uterine rupture during second trimester termination of pregnancy using mifepristone and a prostaglandin. *Eur J Obstet Gynecol Reprod Biol* 1996;65:175–6.
- [124] Norman JE. Uterine rupture during therapeutic abortion in the second trimester using mifepristone and prostaglandin. *Br J Obstet Gynaecol* 1995;102:332–3.
- [125] Sinave C, Le Templier G, Blouin D, Leveille F, Deland E. Toxic shock syndrome due to *Clostridium sordellii*: a dramatic postpartum and postabortion disease. *Clin Infect Dis* 2002;35:1441–3.
- [126] Gonzalez CH, Marques Dias MJ, Kim CA, Sugayama SM, Da Paz JA, Huson SM, et al. Congenital abnormalities in Brazilian children associated with misoprostol misuse in first trimester of pregnancy. *Lancet* 1998;351:1624–7.
- [127] Gonzalez CH, Vargas FR, Perez AB, Kim CA, Brunoni D, Marques Dias MJ, et al. Limb deficiency with or without Mobius sequence in seven Brazilian children associated with misoprostol use in the first trimester of pregnancy. *Am J Med Genet* 1993;47:59–64.
- [128] Fonseca W, Alencar AJ, Mota FS, Coelho HL. Misoprostol and congenital malformations. *Lancet* 1991;338:56.
- [129] Pastuszak AL, Schuler L, Speck Martins CE, Coelho KE, Cordello SM, Vargas F, et al. Use of misoprostol during pregnancy and Mobius syndrome in infants. *N Engl J Med* 1998;338:1881–5.
- [130] Lamberts SW, Koper JW, de Jong FH. The endocrine effects of long-term treatment with mifepristone (RU486). *J Clin Endocrinol Metab* 1991;73:187–91.
- [131] Heikinheimo O, Ranta S, Grunberg S, Lahteenmaki P, Spitz IM. Alterations in the pituitary–thyroid and pituitary–adrenal axes—consequences of long-term mifepristone treatment. *Metabolism* 1997;46:292–6.
- [132] Takiyama Y, Tanaka H, Makino I. The effects of hydrocortisone and RU486 (mifepristone) on iodide uptake in porcine thyroid cells in primary culture. *Endocrinology* 1994;135:1972–9.
- [133] Cameron ST, Thong KJ, Baird DT. Effect of daily low dose mifepristone on the ovarian cycle and on dynamics of follicle growth. *Clin Endocrinol Oxf* 1995;43:407–14.
- [134] Murphy AA, Morales AJ, Kettel LM, Yen SS. Regression of uterine leiomyomata to the antiprogesterone RU486: dose–response effect. *Fertil Steril* 1995;64:187–90.
- [135] Murphy AA, Kettel LM, Morales AJ, Roberts VJ, Yen SS. Regression of uterine leiomyomata in response to the antiprogesterone RU486. *J Clin Endocrinol Metab* 1993;76:513–7.
- [136] Eisinger SH, Meldrum S, Fiscella K, le Roux HD, Guzick DS. Low-dose mifepristone for uterine leiomyomata. *Obstet Gynecol* 2003;101:243–50.
- [137] Laue L, Lotze MT, Chrousos GP, Barnes K, Loriaux DL, Fleisher TA. Effect of chronic treatment with the glucocorticoid antagonist RU486 in man: toxicity, immunological, and hormonal aspects. *J Clin Endocrinol Metab* 1990;71:1474–80.
- [138] Chwalisz K, Stockemann K, Fritzscheier KH, Fuhrmann U. Modulation of oestrogenic effects by progesterone antagonists in the rat uterus. *Hum Reprod Update* 1998;4:570–83.
- [139] Rumpel E, Michna H, Kuhnel W. Morphology of the rat uterus after long-term treatment with progesterone antagonists. *Anat Anz* 1993;175:141–9.
- [140] Bigsby RM, Young PC. Estrogenic effects of the antiprogesterone onapristone (ZK98.299) in the rodent uterus. *Am J Obstet Gynecol* 1994;171:188–94.
- [141] Newfield RS, Spitz IM, Isacson C, New MI. Long-term mifepristone (RU486) therapy resulting in massive benign endometrial hyperplasia. *Clin Endocrinol Oxf* 2001;54:399–404.
- [142] Martineau PA, Levental M. Large endometrial polyp in a patient on long-term mifepristone therapy. *J Ultrasound Med* 2000;19:487–9.
- [143] Murphy AA, Kettel LM, Morales AJ, Roberts V, Parmley T, Yen SS. Endometrial effects of long-term low-dose administration of RU486. *Fertil Steril* 1995;63:761–6.
- [144] Croxatto HB, Kovacs L, Massai R, Resch BA, Fuentealba B, Salvatierra AM, et al. Effects of long-term low-dose mifepristone on reproductive function in women. *Hum Reprod* 1998;13:793–8.
- [145] Heikinheimo O, Ranta S, Grunberg S, Spitz IM. Alterations in sex steroids and gonadotropins in postmenopausal women subsequent to long-term mifepristone administration. *Steroids* 2000;65:831–6.
- [146] Schmidt M, Loffler G. RU486 is a potent inhibitor of aromatase induction in human breast adipose tissue stromal cells. *J Steroid Biochem Mol Biol* 1997;60:197–204.
- [147] Tseng L, Mazella J, Sun B. Modulation of aromatase activity in human endometrial stromal cells by steroids. *Endocrinology* 1986;118:1312–8.
- [148] Croxatto HB, Salvatierra AM, Croxatto HD, Fuentealba B. Effects of continuous treatment with low dose mifepristone throughout one menstrual cycle. *Hum Reprod* 1993;8:201–7.
- [149] Weihua Z, Saji S, Makinen S, Cheng G, Jensen EV, Warner M. Estrogen receptor (ER) beta, a modulator of ERalpha in the uterus. *Proc Natl Acad Sci USA* 2000;97:5936–41.
- [150] Hall JM, McDonnell DP. The estrogen receptor beta-isoform (ERbeta) of the human estrogen receptor modulates ERalpha transcriptional activity and is a key regulator of the cellular response to estrogens and antiestrogens. *Endocrinology* 1999;140:5566–78.
- [151] Zou A, Marschke KB, Arnold KE, Berger EM, Fitzgerald P, Mais DE, et al. Estrogen receptor beta activates the human retinoic acid receptor alpha-1 promoter in response to tamoxifen and other estrogen receptor antagonists, but not in response to estrogen. *Mol Endocrinol* 1999;13:418–30.
- [152] Mulac-Jericevic B, Mullinax RA, DeMayo FJ, Lydon JP, Conneely OM. Subgroup of reproductive functions of progesterone mediated by progesterone receptor-B isoform. *Science* 2000;289:1751–4.