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.

1. Introduction

The first report on RU486 (mifepristone), a progestin and glucocorticoid receptor antagonist, was published by Philibert et al. in 1981\textsuperscript{[1]} . Since then numerous related progesterone receptor ligands have been synthesized \textsuperscript{[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 promoter 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) \textsuperscript{[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\textsuperscript{[5]} and Giangrande and McDonnell \textsuperscript{[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 \textsuperscript{[7–9]} . Initially PAs were divided into Type 1 and Type 2 antagonists. Type 1 antagonists were regarded as “pure” PAs which
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 progestrone. 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, J667, 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. 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-2α 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-2α 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
Clinical applications in medical termination of pregnancy, and endometrial integrity. PAs have the ability to antagonize all to a secretory state and, together with estradiol, maintains proliferative effects on the endometrium, uses in contraception as well as in other gynecological and non-gynecological conditions.

### 2.1. Short-term administration

#### 2.1.1. Medical termination of early pregnancy 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 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].

### Table 1

<table>
<thead>
<tr>
<th>Application</th>
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<tr>
<td>Medical termination of early pregnancy</td>
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<tr>
<td>Medical termination of more advanced pregnancies</td>
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<td>Menstrual regulation</td>
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<td>Labor induction (not recommended)</td>
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<td>Medical management of early fetal demise</td>
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<td>Management of fetal death</td>
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<td>Emergency contraception</td>
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### 2.1.2. Longer-term administration

Long-term administration

<table>
<thead>
<tr>
<th>Condition</th>
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<tr>
<td>Uterine myoma (PRMs or Pas)</td>
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<tr>
<td>Endometriosis (PRMs or Pas)</td>
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<tr>
<td>Contraception (PAs)</td>
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<tr>
<td>Non-gynecological applications of PAs</td>
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#### GeneSwitch® system for ligand-dependent transgene expression

- Cushing’s syndrome
- Glucocorticoid antagonism (potential application in burns, glucocorticoid-dependent hypertension, arthritis, glaucoma, viral diseases possibly including AIDS)
- Major depression with psychotic features
- Alzheimer’s disease
- Steroid receptor containing tumors (breast, ovary, prostate and endometrium as well as in meningiomas, gliomas and leiomyosarcomas)

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.

### 2.1.3. Potential use in IVF programs

- Emergency contraception
- Management of fetal death
- Medical management of early fetal demise
- Labor induction (not recommended)
- Menstrual regulation
- Medical termination of more advanced pregnancies
- Medical termination of early pregnancy

### 2.1.4. Other applications

- Contraception (PAs)
- Endometriosis (PRMs or Pas)
- Uterine myoma (PRMs or Pas)
- Potential use in IVF programs
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 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 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

![Logistic regression model analysis](image-url)
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]. Recently, 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>
<thead>
<tr>
<th>Regimen</th>
<th>Efficacy (%)</th>
<th>Study</th>
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<tbody>
<tr>
<td>Mif 600 mg, Miso 400 μg, 200 μg, 2 h apart (O)</td>
<td>93</td>
<td>[64]</td>
</tr>
<tr>
<td>Mif 600 mg</td>
<td>82</td>
<td>[61]</td>
</tr>
<tr>
<td>Mif 200 mg, After 36–48 h, 3 sequential doses of Miso (O)</td>
<td>89</td>
<td>[63]</td>
</tr>
<tr>
<td>Mif 400 mg, After 36 h, Miso 400 μg (O)</td>
<td>52</td>
<td>[66]</td>
</tr>
<tr>
<td>Mif 200 mg, After 36–48 h, Miso 800 μg (V), 200 μg, 400 μg (V/O) at 3 h intervals</td>
<td>84</td>
<td>[65]</td>
</tr>
<tr>
<td>Mif 200 mg (O)</td>
<td>88</td>
<td>[62]</td>
</tr>
<tr>
<td>Mif 200 mg (O), After 36–48 h, Miso 800 μg (S), 400 μg (S), 400 μg (S) at 3 h intervals</td>
<td>84</td>
<td>[67]</td>
</tr>
<tr>
<td>Mif 600 mg (O), After 48 h, Miso 400 μg (V) and 200 μg (V) at 2 h intervals</td>
<td>74</td>
<td>[67]</td>
</tr>
<tr>
<td>Miso 0.4 μg (V)</td>
<td>71</td>
<td>[67]</td>
</tr>
</tbody>
</table>

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 ovud [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 progestosterone 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 J3867. 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 J3867 were administered for 12 weeks. J3867 reduced myoma and uterine volume as well as the intensity and duration of menstrual 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-κB 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 J3867, 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 Cushinoid 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].

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 [117]. 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 microscopical 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 dysynchronous and reminiscent of an unopposed estrogen effect. There was, however, no conclusive evidence of endometrial 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. ERβ is antiproliferative in several models [149] and often functions as a transdominant repressor of ERα transcriptional activity [150]. Since mifepristone can act as a potent ERβ antagonist [151], this leaves the ERα 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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