Effect of low daily doses of mifepristone on ovarian function and endometrial development

K.Gemzell Danielsson1, M.-L.Swahn1, P.Westlund2, E. Johannisson3, M.Seppälä4 and M.Bygdeman1,5

Department of Woman and Child Health, 1Division for Obstetrics and Gynecology and 2Division for Reproductive Endocrinology, Karolinska Hospital, S-171 76 Stockholm, Sweden. 3Hôpital Cantonal, Geneva, Switzerland and 4Department of Obstetrics and Gynecology, Central University Hospital, Helsinki, Finland

5To whom correspondence should be addressed

The effects of low daily doses of the antiprogestin mifepristone (RU 486) on ovarian and endometrial function were studied. The study included one control cycle, three treatment cycles and one follow-up cycle. During the treatment cycles, either 0.1 (n = 5) or 0.5 (n = 5) mg of mifepristone was administered once daily. Urine samples were collected three times weekly during the control and treatment cycles and pregnanediol glucuronide and oestrone glucuronide and luteinizing hormone (LH) were quantified by radioimmunoassay. Blood samples for cortisol measurement were collected once weekly and for serum glycodelin at the onset of menstruation. An endometrial biopsy was obtained in the mid-luteal phase in the control cycle and in the first and third treatment cycles and analysed by morphometric and histochemical methods. Binding of Dolichus biflorus agglutinin (DBA) lectin was measured and expression of progesterone and oestrogen receptors and glycodelin were analysed immunohistochemically. All cycles studied were ovulatory with an LH peak and elevated pregnanediol glucuronide concentrations. Follicular development seemed normal as judged by ultrasound examination. The length of the menstrual cycle and the menstrual bleeding were not significantly altered. Following administration of 0.5 mg mifepristone/day, endometrial development appeared to be slightly retarded and glandular diameter was significantly reduced. Furthermore, significant decreases in DBA lectin binding and endometrial expression of glycodelin were observed. Daily doses of 0.1 mg did not have any significant effect on the endometrium. No differences in oestrogen or progesterone receptor immunoactivity between control and treatment cycles were seen. This study provides further evidence that endometrial function is sensitive even to doses of antiprogestin that are low enough not to disturb ovulation. It remains to be established whether these effects are sufficient to prevent implantation.

Key words: antiprogestin/endometrial receptivity/glycodelin/implantation/ovulation

Introduction

Mifepristone (RU 486) is a potent antigestagen that blocks progesterone action at the receptor level (Philibert et al., 1982). The effects of mifepristone depend on the dose given and the stage of the menstrual cycle. Throughout the follicular phase mifepristone has little, if any, effect on the endometrium but gonadotrophin concentrations, follicular development and ovulation are suppressed (Liu et al., 1987; Shoupe et al., 1987b; Swahn et al., 1988). Immediately after ovulation, the formation of corpus luteum is not affected, but the development of secretory endometrium is retarded (Swahn et al., 1990). Later, during the luteal phase, bleeding occurs due to an effect on the endometrium, while luteal regression occurs inconsistently (Schaison et al., 1985; Shoupe et al., 1987a; Garzo et al., 1988; Swahn et al., 1988). During pregnancy, mifepristone acts on the decidua (Schindler et al., 1985) and also induces myometrial activity, as well as increasing myometrial sensitivity to prostaglandins (Swahn and Bygdeman, 1988).

The various effects of antiprogestins on the hypothalamic–pituitary system and the endometrium may be useful for contraceptive purposes by inhibiting ovulation, preventing or disrupting implantation or by inducing luteal regression and menstrual bleeding. To date, mifepristone has been used as an effective postcoital method of contraception (Glaiser et al., 1992; Webb et al., 1992) and in the early luteal phase as a once-a-month pill (Gemzell Danielsson et al., 1993). If the endometrium is more sensitive to the antiprogestagenic effect of mifepristone compared to the ovary or the hypothalamic–pituitary system, it is possible that a low-dose regimen could be developed that would inhibit endometrial maturation and prevent implantation, without disturbing ovulation and the normal rhythm of the menstrual cycle. Intermittent or daily treatment would be more practical than once-a-month treatment, and would preclude failure due to possible individual variations in the receptive phase.

The aim of the present study was to evaluate this possibility. A low dose of mifepristone, 0.1 or 0.5 mg, was administered daily and the effect on ovarian function and endometrial development and function was studied.

Materials and methods

Subjects

In all, 10 healthy women were studied after giving informed consent. They were all menstruating regularly, aged 27–40 (mean 35) years, weighed 59–70 (mean 66) kg, and 0–6 (mean 3) gravida, 0–3 (mean 1.8) para. The study was approved by the ethics committee at the Karolinska Hospital, Sweden.
None of the women had used steroidal contraceptives or an intrauterine device for a minimum of 3 months prior to the study. Gynaecological examination was performed on admission. The subjects, who were not sterilized, were advised to use barrier methods for contraception during the study and all subjects were asked to keep daily records on any side-effects and bleeding. Serum chemistry analyses were done at admission and at the end of treatment.

The study included one control cycle, three treatment cycles and a follow-up cycle. During the treatment cycles, mifepristone (RU 486; Roussel Uclaf, Paris, France) was administered as daily oral doses of either 0.1 mg (n = 5) or 0.5 mg (n = 5) at 21.00 h. The follicular phase was defined as the period between the first day of menstrual bleeding (cycle day 1) and the day of urinary lutetinizing hormone (LH) peak, both days inclusive. The luteal phase was defined as the period between cycle day LH+1 and the day prior to the next menstrual period, both days included. Follicular growth was monitored once weekly by pelvic ultrasonography.

**Hormone determinations**

Morning urine was collected three times weekly during control and treatment cycles. The samples were analysed for pregnanediol glucuronide, oestrone glucuronide and LH using radioimmunoassay (Cekan et al., 1986). Hormone concentrations in the urine were expressed per gram of creatinine (Metcalfe and Hunt, 1976). For creatinine analysis, a commercial kit (Sigma Diagnostics, St Louis, MO, USA, procedure no. 555) was used. In addition, all subjects determined the LH peak in urine samples collected twice daily from approximately cycle day 10 to day LH+2 by using a rapid self-test (Clearplan; Searle Unipath Ltd., Bedford, UK).

The individual steroid concentrations were normalized around the day of the LH peak, and the area under the curve was calculated by the trapezoidal method for each subject and cycle for the following periods: pregnanediol glucuronide from LH+1 to LH+11, and oestrone glucuronide and LH from LH–5 to LH+5.

Once weekly during treatment, at about 9.00 h, a blood sample was obtained for measurement of cortisol (Sutf et al., 1986). Serum concentrations of glycodelin (Dell et al., 1995) were measured once monthly at onset of menstruation by immunofluorometric assay (Kämäräinen et al., 1994).

**Endometrial biopsy**

Using a Randall curette, an endometrial biopsy was obtained from the fundus and upper part of the uterus. A biopsy was taken in control, first and third treatment cycles on one of the cycle days LH+5 to LH+8 according to the LH self-test. No cervical dilatation or local anaesthesia was used. The endometrial material was assessed by morphometric and histochemical analyses.

**Morphometric analyses**

One part of the biopsy material was immediately fixed in Bouin’s solution and used for light microscopic examination (×400) after embedding in paraffin wax and staining with haematoxylin. Morphometric analyses were performed, measuring the number of glands per mm², the number of glandular and stromal mitoses per 1000 glandular or stromal cells respectively, glandular diameter (mm), glandular epithelial height (mm), the number of cells with basal vacuolization per 1000 glandular cells, the number of pseudostratified cells, as well as the degree of stromal oedema, predecidualization and leukocyte infiltration. The findings were used to determine the degree of development of the endometrium and described as the day of the cycle according to Johannisson et al. (1987). Microscopic evaluation of the samples was performed at the end of the study by one person who was unaware of the precise cycle day and whether the biopsy had been taken in a control or a treatment cycle.

**Immunoo- and lectin histochemistry**

A second portion of each biopsy was immediately frozen in liquid nitrogen and kept at –70°C. It was then mounted in an embedding medium which, in addition to non-reactive ingredients, contained 10.24% polyvinyl alcohol and 4.26% polyethylene glycol (O.C.T. Compound; Miles Inc., Elkhart, IN, USA) at –17°C and sectioned to 8–10 mm using a Reichert–Jung Cryocut 1800 (Cambridge Instruments GmbH, Nussloch, Germany). The sections were placed on glass slides and air dried for 15–20 min before a 10 min fixation in acetone. Thereafter, the mounted sections were wrapped in Parafilm and stored at –70°C until processed for immuno- or lectin histochemistry.

Progestrone receptors (PR) were detected using the Abbot PGR-ICA monoclonal assay system (Abbot Laboratories Inc., North Chicago, IL, USA). Localization of oestrogen receptors (ER) was performed with monoclonal antibody ER1D5 (Immunotech. SA, Marseilles, France) and the Vectastain Elite ABC immunoperoxidase detection system (Vector Laboratories Inc., Burlingham, CA, USA) according to the instructions of the manufacturer.

The secretory components of the endometrium were detected by lectin histochemistry using biotinylated Dolichos biflorus agglutinin (DBA) lectin at a concentration of 5 µg/ml and the Vectastain Elite ABC immunoperoxidase detection system (Vector Laboratories Inc.). DBA binds to N-acetylgalactosamine and galactose residues present in the glandular secretion of the mid-luteal phase endometrium (Mazur et al., 1989). As a negative control, DBA was co-incubated with the corresponding carbohydrate ligand at 200 mM concentration, which completely inhibited the binding.

For the staining of glycodelin, tissue sections were treated with phosphate-buffered saline (PBS) containing Tween 20 (0.005%) for 10 min at room temperature and then incubated with normal porcine serum 1:10 in PBS for 20 min. Immunofluorinity purified polyclonal antibody against human glycodelin (Kämäräinen et al., 1996) was applied (5 µg/ml) for 1 h at room temperature. After incubation, the slides were washed three times in PBS for 2 min. Specific binding of the primary antibody was detected using a complex of biotinylated porcine anti-rabbit immunoglobulins (Dako, E 353) diluted 1:300, for 40 min. The slides were washed three times with PBS for 2 min each, incubated with 0.6% hydrogen peroxide in methanol for 5 min to block endogenous peroxidase activity, and then washed again three times for 2 min each in PBS prior to incubation for 30 min with avidin–biotin complex/animal peroxidase (Dako Laboratories, Copenhagen, Denmark, code no. K 355) prepared according to the instructions. After three periods of 2 min each in PBS, the peroxidase substrate solution 3-amino-9-ethylcarbazole (ACE; Sigma Products, St Louis, MO, USA) was added. When incubated for 5 min the sections were rinsed with tap water, counterstained with 25% Meyers haematoxylin (Kebo, Stockholm, Sweden) for 90 s, and mounted with coverslips. Sections of human first trimester decidua were used as a positive control. As a negative control, the rabbit anticygodelin antiserum was replaced with the immunoglobulin (Ig) G fraction of normal rabbit serum or with PBS.

Immunoo- and lectin histochemical stainings were evaluated blindly by two independent persons, using a Zeiss light microscope at ×200 magnification. Observations were made in various, non-overlapping fields of the whole section in two or three labelling experiments and included stromal, luminal and glandular cells. The cells were assigned a score of 0 to 4 based on the number of cells specifically stained as follows: 0 (0% positive cells); 1; very weak (<3% positive cells); 2, weak (5–25% positive cells); 3, moderate (25–75% positive cells); or 4, strong (>75% positive cells). A similar scoring system has
been used by Press et al. (1988). The occurrence of specific staining for glycodelin was scored as absent (−), weak (+), moderate (++) or intense (+++).

Statistics
A log-normal distribution was assumed for the steroid hormones and LH concentrations (Gaddum, 1945). The paired t-test was used for evaluating differences in urinary hormone concentrations between the control and treatment cycles. Differences in morphometric parameters, receptor concentrations, DBA-lectin binding, glycodelin concentrations and the length of the menstrual cycles and bleeding were evaluated by using the two-tailed Wilcoxon’s signed ranks test. A P value < 0.05 was considered statistically significant. The hormonal values are presented as geometric means with 95% confidence limits.

Results

Folliculogenesis, ovulation and cycle length
All control and treatment cycles were ovulatory, with an LH peak and elevated progesterone concentrations and with follicular development judged by ultrasound. The length of the control cycle was 23–28 days. No statistical difference could be found in cycle length between control, treatment and follow-up cycles. However, one woman, while suffering from influenza, experienced a prolonged follicular phase (27 days) during the second month of daily treatment with 0.5 mg mifepristone, while the length of her luteal phase was unchanged (11 days). This woman completed only two treatment cycles and hence her second biopsy was taken during the second treatment month. The duration of menstrual bleeding (4–7 days) and subjectively evaluated blood loss were unaffected by treatment. No irregular bleeding or spotting were noted, and the results of serum chemistry analyses were within the normal range and did not differ from control values. Two patients taking the higher dose complained of acne during the first treatment month. In these subjects there were no problems during the following treatment cycles. No other side-effects were observed.

Hormone concentrations
An LH peak was detected by the self-test in all control and treatment cycles. This was also confirmed by the laboratory analyses. There was no statistical difference in the height of the LH peak (Figure 1). Urinary concentrations of oestrone glucuronide and pregnanediol glucuronide were not significantly affected by the treatment. Plasma cortisol concentrations were within the normal range and did not differ between the control and treatment cycles.

Endometrial morphometric analyses
In the control cycles, there was an excellent relationship between the calculated cycle day based on the LH peak and the histological dating of endometrial biopsies by morphometric analyses (Table I). Following treatment with 0.1 mg/day, the endometrium did not differ from the normal secretory appearance of the controls. In the higher dose group, all the parameters included in the morphometric analysis, except for glandular diameter, were unchanged. The diameter of the glands was significantly reduced (P < 0.05) from a mean of

Glycodelin in serum
Serum concentration of glycodelin was measured at the time of menstruation (cycle day 1 ± 2 days) and was in the range of values previously reported, 22.4–74.5 µg/l (mean 45.0), (Seppäla et al., 1987; Swahn et al., 1993; Gemzell Danielsson et al., 1996). Serum glycodelin concentrations were not affected by 0.1 mg mifepristone daily. In the higher dose group, serum glycodelin concentrations decreased slightly in four of the women (range 5.2–70.7 µg/l, mean 23.3) but increased (~2-fold) in one woman. In the latter subject, endometrial expression of glycodelin was abolished during treatment with 0.5 mg mifepristone/day.

Endometrial expression of glycodelin
In control biopsies obtained on one of the cycle days LH +5–8 (mean 7.2), all but one specimen showed positive staining for glycodelin localized within the glandular lumen. During the first treatment month with 0.1 mg mifepristone daily, no changes could be found, while the serum glycodelin concentration seemed to have decreased in the third treatment
Table I. Morphometric dating of endometrial biopsies in control and treatment cycles (0.5 mg of mifepristone daily for 3 months)

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Biopsy datea</th>
<th>Morphometric dating</th>
<th>Biopsy datea</th>
<th>Morphometric dating</th>
<th>Biopsy datea</th>
<th>Morphometric dating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td></td>
<td></td>
<td>Mifepristone, 0.5 mg daily</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>1st month</td>
<td>3rd month</td>
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<tr>
<td>1</td>
<td>+6</td>
<td>+6</td>
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<td>+5</td>
<td>+4/5</td>
<td>+8</td>
<td>+6/7</td>
<td>+5</td>
<td>+5/6</td>
</tr>
</tbody>
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4Days after urinary luteinizing hormone peak.
5Insufficient material.
6Second biopsy taken during second month (see text).

Table II. Dolichus biflorus agglutinin staining intensity in endometrial glandular epithelium in control cycles and in treatment cycles in which 0.1 or 0.5 mg of mifepristone was administered once daily for 3 months (n = 5 in each treatment group)

<table>
<thead>
<tr>
<th>Mifepristone dose (mg)</th>
<th>Mean (range) labelling score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control cycle</td>
</tr>
<tr>
<td>0.1</td>
<td>3.4 (3–4)</td>
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<tr>
<td>0.5</td>
<td>3.2 (3–4)</td>
</tr>
</tbody>
</table>

4One patient had the second biopsy taken during the second month (see text).
6p < 0.01 (control compared to treatment months).

Table III. Endometrial glycodelin in control and mifepristone-treated cycles as detected immunohistochemically

<table>
<thead>
<tr>
<th>Subject</th>
<th>Presence of glycodelina</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>0.1 mg mifepristone</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>++</td>
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<tr>
<td>2</td>
<td>+++</td>
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<tr>
<td>3</td>
<td>++++</td>
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<tr>
<td>4</td>
<td>++</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
</tr>
<tr>
<td>0.5 mg mifepristone</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>++</td>
</tr>
<tr>
<td>7</td>
<td>+++</td>
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<tr>
<td>8</td>
<td>++</td>
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<tr>
<td>9</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>–</td>
</tr>
</tbody>
</table>

6Cells were assigned a score as follows: – = absent, + = weak, ++ = moderate, +++ = intense.
8One patient receiving 0.5 mg mifepristone had the second biopsy taken during the second month (see text).

Discussion

Since progesterone is necessary for the establishment and maintenance of pregnancy, antiprogestins such as mifepristone could be expected to have a number of effects on reproductive events. Today, mifepristone in combination with a prostaglandin is a well accepted and effective non-surgical method for termination of early pregnancy (see Bygdeman, 1995). Studies on the effect of mifepristone on the menstrual cycle have shown that this agent, by blocking the PR, could interfere with both the ovarian and the endometrial function, depending on the dose and time of administration. Ovulation can be consistently suppressed by continuous administration of mifepristone in doses as low as 2 mg/day (Ledger et al., 1992; Croxatto et al., 1993) or 10 mg once a week (Spitz et al., 1993). It has previously been shown that treatment with a high dose of mifepristone (200 g) on day LH + 2 will result in lack of endometrial secretory activity, inhibited expression of 17β-hydroxysteroid dehydrogenase, inhibited down-regulation of PR (Gemzell Danielsson et al., 1994; Mäentausa et al., 1993), decreased concentrations of prostaglandin F2α in uterine fluid (Gemzell Danielsson and Hamberg, 1994) and subnormal serum concentrations of glycodelin (Gemzell Danielsson et al., 1996), as well as increased myometrial activity at the expected time of implantation (Gemzell et al., 1990). Stimulated myometrial activity may also contribute to desynchronization between embryo and endometrium (Psychoyos and Prapas, 1987). Even much lower doses of mifepristone (down to 1.0 mg) have been shown to be sufficient to inhibit endometrial development and function, but they do not inhibit ovulation (Batista et al., 1992; Croxatto et al., 1993). These effects of various doses of mifepristone on its main target organs make it potentially useful for contraceptive purposes, either by its effects on folliculogenesis and ovulation (Baird et al., 1995; Croxatto et al., 1995; Kekkonen et al., 1995) or by a direct effect on endometrium, decidua or corpus luteum to prevent implantation or interrupt early pregnancy. To date, mifepristone has only been shown to be effective for contraception when used as an emergency postcoital method (Glassier et al., 1992; Webb et al., 1992) or on a regular basis in the early luteal phase as a once-a-month pill (Gemzell Danielsson et al., 1993). There are now results indicating a dissociation between the central effects of mifepristone on gonadotrophin-dependent folliculogenesis–ovulation and the direct effect on the endomet-

cycles. The effect was more pronounced after treatment with the higher dose of 0.5 mg per day (P < 0.05; Table III and Figure 2). The single negative control sample was collected on day LH + 6. This subject had a weak (+) positive staining for glycodelin in her first treatment cycle (0.5 mg/day) when the biopsy was obtained on cycle day LH + 7. In the last treatment cycle, the endometrial tissue was collected on LH + 6 and no staining was seen.
Figure 2. Glycodelin located in glandular epithelium in control cycle (A) and following treatment with 0.5 mg mifepristone for 3 months (B). The endometrial specimens were obtained on cycle day LH+7 in both cycles. Original magnification ×125.

This opens the possibility for the development of a low-dose regimen that would inhibit endometrial function without blocking ovulation. In the present study, a daily dose of either 0.1 or 0.5 mg mifepristone was given for three consecutive cycles without disturbing ovulation or the normal menstrual cycle rhythm. Urinary concentrations of pregnanediol glucuronide and oestrone glucuronide after treatment remained...
unchanged. Treatment with the higher dose caused a slight but obvious retardation of endometrial maturation at the expected time of implantation. This was reflected by decreased glandular diameter. In agreement with the histological changes, there was a reduced DBA binding to the endometrial glands, indicating a reduced secretory activity. Even a minor change in secretory activity may result in lack of implantation, since successful implantation depends on synchronization between the embryo and the development of a receptive endometrium (Davies et al., 1990). The importance of precisely timed functioning of the endometrium is further supported by the studies of Lessey et al. (1995), who investigated the expression of integrins as markers of endometrial maturation and uterine receptivity.

Glycodelin (Dell et al., 1995), also known as placental protein 14, is a glycoprotein with immunosuppressive and contraceptive activities (Julkunen et al., 1988; Okamoto et al., 1991; Oehninger et al., 1995). In the endometrium, glycodelin is secreted into the glandular lumen and uterine fluid around the peri-implantation period. Glycodelin concentrations in serum start to rise in the mid-luteal phase, reaching a maximum at the onset of the next menstrual period. If the luteal phase is inadequate, the circulating concentrations are lower (Joshi et al., 1986). Reduction in serum glycodelin following treatment with mifepristone has previously been reported (Gemzell-Danielsson et al., 1996), and following treatment with mifepristone in combination with tamoxifen (Swahn et al., 1993). However, measurements of circulating concentrations of glycodelin do not seem to predict a receptive endometrium (Wood et al., 1990), and recent evidence also indicates that glycodelin is not endometrium-specific. It is synthesized in haematopoetic tissues of the bone marrow (Kämäräinen et al., 1994) and perhaps other tissues. A more valuable method of assessing endometrial function might be to analyse glycodelin expression in an endometrial biopsy or in uterine fluid (Rizk et al., 1992; Mackenna et al., 1993). Measurement of glycodelin in endometrial tissue or uterine fluid may better reflect endometrial function than the concentration in plasma, since influence by extraterine sources of the protein is avoided.

In the present study, serum glycodelin decreased during treatment with 0.5 mg mifepristone per day, except for one subject, in whom serum concentrations increased. In this subject, endometrial glycodelin was abolished by mifepristone treatment. The increased serum concentrations may thus have been due to the increased extraterine release of glycodelin. The endometrial expression of glycodelin was significantly decreased following daily administration of 0.5 mg mifepristone. An explanation for the single glycodelin-negative control biopsy is probably that this biopsy was obtained too early (cycle day LH+6). The same woman had a weak positive biopsy during the first treatment month when the biopsy was collected on day LH+7. The results of this study lend further support to the view that progesterone plays a role in endometrial glycodelin synthesis.

In a previous study, mifepristone was given as an intermittent low dose of 2.5 or 5 mg once a week for 2 months, starting on cycle day 2 (Gemzell-Danielsson et al., 1996). Ovulation was not inhibited but could occasionally be delayed for 6–13 days. The length of the luteal phase was unaffected. A dose of 5 mg of mifepristone once a week was sufficient to disturb endometrial development and secretory activity significantly and to inhibit the down-regulation of PR normally occurring during the luteal phase. Endometrial morphology, PR concentration and serum concentrations of glycodelin were affected to a lesser extent with the lower dose. That the effect of low-dose treatment with mifepristone on the endometrial function observed in this and the previously mentioned study could prevent implantation is supported by the results of Katkam et al. (1995), who studied the effect of the antiprogestin onapristone (ZK 98,299), given in low intermittent doses to bonnet monkeys. Four animals treated with 2.5 mg onapristone for 17 cycles and another four treated with a 5 mg dose for 21 cycles did not conceive, while one animal treated with 5 mg became pregnant in the first treatment cycle. In the majority of cycles, ovulation was not disturbed but anovulation and luteal insufficiency occurred in some animals during prolonged treatment. Endometrial biopsies from 8 days after the midcycle oestradiol peak showed retardation with decreased glandular diameter.

It is unlikely that the skin problem noted by two women treated with 0.5 g/day could be a direct result of the treatment because no problems with acne were noted for daily treatment with 200 mg mifepristone in 10 patients with meningeomas (Lamberts et al., 1991). Furthermore, mifepristone has very low affinity for the androgen receptor and it does not bind to transcortin or sex hormone-binding globulin (Moguilewsky and Philibert, 1985). The doses of mifepristone required to produce antiglucocorticoid effects are higher than those needed for anti-progestagenic activity (Shoupe et al., 1987a). Treatment with 2–10 mg mifepristone for 30 days had no effect on the peripheral concentration of cortisol or adrenocorticotropic hormone (Ledger et al., 1992; Croxatto et al., 1993), and serum cortisol was not affected by mifepristone treatment in the present study.

It is believed that progestins suppress oestrogen action in the endometrium by down-regulating ER. Daily treatment with 50 mg mifepristone for 6 months resulted in increased ER concentrations in the stroma and cystic changes consistent with oestrogenic effects (Murphy et al., 1995). The significance of this ‘unopposed oestrogen’ effect during treatment with antiprogestin needs to be investigated further. However, both onapristone and mifepristone have the ability to antagonize the action of oestrogen on the endometrium in primates (Van Uem et al., 1989). The immunoreactivity of ER and PR was unchanged after mifepristone treatment in the present study, and no signs of endometrial stimulation were found.

The present study clearly shows that endometrial secretory activity is sensitive even to such low doses of an antiprogestin that do not disturb ovarian function and ovulation. Furthermore, the concentrations of ER and PR were unaffected by the treatment and no signs of endometrial stimulation were recorded. It remains to be shown that the effects observed here on endometrial secretory activity also inhibit endometrial receptivity and implantation.
Acknowledgements

The mifepristone tablets were kindly prepared and supplied by Roussel Uclaf, Paris, France, in collaboration with Professor Etienne Baulieu, Paris, France, who also initially suggested the study. The authors are grateful to the WHO/HRP Task Force on Post-Ovulatory Methods for Fertility Regulation for valuable advice and suggestions when the study was planned. We would also like to thank our research staff, and Astrid Hägglund for typing the manuscript. Financial support from the Knut & Alice Wallenberg Foundation and the Swedish Medical Research Council is gratefully acknowledged. The measurement of glycodeolin was supported by grants from the Academy of Finland, Finnish Cancer Foundation and Finnish Life and Pension Insurance Companies.

References


Antiprogestin and endometrial receptivity


Received on July 1, 1996; accepted on October 10, 1996