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OUTSTANDING CONTRIBUTION

Effects of long-term low-dose mifepristone on reproductive function in women

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Low-dose antiprogestin administration has been proposed as a new contraceptive modality to interference with endometrial receptivity without disturbing ovarian function. The effects of 1 mg/day mifepristone for 150 days on the menstrual cycle were assessed in 21 surgically sterilized women. The aim was to study each woman for one control cycle and during months 1, 3 and 5 of treatment. Ovulation, endometrial thickness, serum oestradiol and progesterone, urinary luteinizing hormone, endometrial morphology and cervical mucus were assessed. Luteal phase progesterone concentrations were observed in 36 of the 60 treated months assessed and less frequently as treatment progressed. The bleeding pattern was regular in most biphasic cycles, while prolonged interbleeding intervals or no bleeding were associated with monophasic cycles. Altered endometrial morphology was found in all cases irrespective of the occurrence of luteal activity. Increased endometrial thickness and dilated glands were observed in 25 and 34% respectively of the monophasic cycles. Mifepristone, 1 mg/day, interferes with endometrial development while allowing the occurrence of biphasic ovarian cycles and regular bleeding. However, it also prevents ovarian cyclicity in a high proportion of treated months, and this is associated with increased endometrial growth in some women, which may be of concern.

Key words: antiprogestin/endometrial contraception/mifepristone/ovarian cycle/women

Introduction

The effects of progesterone blockade by mifepristone administration during the menstrual cycle in women indicate that antiprogestins may be used to inhibit ovulation and/or to prevent implantation (for recent reviews see Van Look and von Hertzen, 1995; Spitz *et al.*, 1996). Preliminary trials have shown that daily mifepristone administration throughout one menstrual cycle inhibited ovulation and altered endometrial development when doses ⩾2 mg/day were used (Ledger *et al.*, 1992; Croxatto *et al.*, 1993; Cameron *et al.*, 1996). A differential threshold for mifepristone effects on the ovary and the endometrium was observed when 1 mg/day was given (Croxatto *et al.*, 1993). With this dose, endometrial development was consistently altered and ovarian function was preserved in most cases (Batista *et al.*, 1992; Croxatto *et al.*, 1993). This differential threshold would theoretically allow for inhibition of endometrial development and function, thus preventing implantation, while ovarian function and bleeding cyclicity would be preserved. To explore this hypothesis, a two-centre trial was conducted to assess the effects of 1 mg/day mifepristone for 5 months on ovarian function, endometrial development and bleeding cyclicity. The recent publication of a similar study performed utilizing 0.5 or 0.1 mg/day mifepristone (Gemzell-Danielsson *et al.*, 1997) complements the findings reported here.

Materials and methods

The study was approved by the ethics committee at the Albert Szent-Györgyi Medical University (Szeged, Hungary) and at ICMER (Santiago, Chile). Each volunteer gave written informed consent before being enrolled in the study. A total of 23 healthy, surgically sterilized women volunteered for the study: 11 at Szeged, Hungary and 12 at Santiago, Chile. Mean age, height and weight were 34.6 years (range 25–39), 158.4 cm (range 150–168) and 59.8 kg (range 50–85) respectively. A medical and gynaecological examination, routine serum chemistry analysis and haematological investigation were performed at admission and at the end of the study.

One woman discontinued voluntarily during the control cycle. Therefore only 22 of the 23 women began treatment, and 19 of these completed the study. Each woman who completed the study participated for one control cycle and one 150 day treatment period. One woman contributed to the study with only 120 days and another with only 60 days of treatment; their data were included in the analysis. One woman was excluded from further analysis after an abnormal control cycle was detected. Altogether 101 months of treatment were accrued by 21 women. Treatment started on day 1 of the cycle, immediately after the control cycle. During treatment, the subjects received 1 mg/day mifepristone orally, between 6:00 and 10:00 h. The endpoint variables were assessed during the control cycle and months 1, 3 and 5 of treatment. All subjects were asked to keep daily records of pill intake time, bleeding and spotting episodes, complaints and other medications.

Ovarian function assessment

Ovarian function was evaluated according to the growth and rupture of the leading follicle and the concentration of oestradiol and

progesterone in the plasma. Follicular growth and the occurrence of ovulation were assessed by ultrasonography twice a week during the control cycle and three times a week during months 1, 3 and 5 of treatment using an Aloka SS D 620 (Tokyo, Japan) with a 5 mHz vaginal probe or a Hitachi EUB 450 (Tokyo, Japan) with a 7.5 mHz vaginal probe.

Blood samples, 10 ml each, were obtained on the same days as echographic monitoring. The concentrations of oestradiol and progesterone in the plasma and of luteinizing hormone (LH) in the urine were measured by a radioimmunoassay, according to the procedures and with the reagents supplied by the World Health Organization (WHO).

Assessment of endometrial development

Endometrial thickness was measured by ultrasound on the same days of follicular growth assessment. Measurements were performed in the sagittal plane, across the upper third, from one basal layer to the other. The thickness of the luminal fluid image, when present, was subtracted from the measurement (Scott, 1994). Endometrial biopsies were taken with a cannula (GynoSampler, GynoFarma) or a 5 mm Randall curette during the control cycle and during months 1, 3 and 5 of treatment. The study protocol prescribed that the biopsy should be taken: (i) on days 22–24 of the pretreatment cycle; and (ii) 8–10 days after an LH peak or on days 22–24 of an LH peak-free interval, whichever came first, during months 1, 3 and 5 of treatment. To time the endometrial sampling according to the LH peak, volunteers collected daily the first morning urine sample.

In the control cycles 21 endometrial biopsies were taken: 16 on days 7–10 after follicular rupture, and five on days 1, 4, 5, 11 and 12 after follicular rupture. During the first month of treatment 21 biopsies were taken: 15 on days 20–24 and six on days 25–28 of treatment. In the third month 18 biopsies were taken: 15 on days 83–86 and three on days 79–80. In one subject the biopsy was taken on day 92 of treatment, and in another no biopsy was taken. During the fifth month 16 biopsies were taken: 10 on days 143–147, four on days 134–142 and two on days 148–149 of treatment. In four subjects no biopsy was taken during this month. Part of each tissue sample was fixed in 10% buffered formalin and embedded in paraffin. Tissue sections were stained with haematoxylin–eosin to assess endometrial histology. The remaining tissue samples were processed for steroid receptor immunocytochemistry (results not reported here).

Endometrial dating was performed according to the criteria of Noyes *et al.* (1950) at each centre. Later on, all samples were reviewed by the pathologist at Santiago (H.D.C.). Samples that did not fit with Noyes's criteria were classified as follows: (i) secretory irregular: uneven glandular growth, with or without intraluminal secretion, and with varying degrees of stromal oedema, with rare slight-to-moderate predecidual reaction; (ii) secretory delayed: secretory pattern that does not correspond to the histological picture of the endometrium expected according to the post-LH peak interval; (iii) mixed: proliferative and secretory signs in different endometrial glands; or (iv) involuted: small glands exhausted of secretory material, lined with cuboidal or low columnar eosinophilic epithelium; the appearance of the stroma is variable, but almost always displays some degree of oedema.

Cervical mucus

Cervical mucus samples were taken two or three times a week before the ultrasound examination during the control cycle and months 1 and 5 of treatment in a subgroup of 11 women. Evaluation included the assessment of the amount, consistency, spinnbarkeit, ferning and cellularity, according to the procedure described by WHO (1987). The scale for each variable was from 0 to 3, allowing a maximum total score of 15.

Data analysis

In the analysis of the data the following end-points and definitions were used: (i) length of the cycle: cycle length was calculated counting from day 1 of menses until the day preceding the next menstrual-like bleeding, both inclusive (if it lasted >90 days it was considered amenorrhoea); (ii) retrospective timing of the endometrial biopsy: the day of the cycle in which each endometrial biopsy taken was related to day 1 of the luteal phase, unless it was taken in the follicular phase. The first day in which the follicular echo-image disappeared was designated day 1 of the luteal phase. Usually this day coincided with the day of the LH peak in urine. Therefore LH peak in urine, followed by at least a doubling of progesterone concentrations, was used in some instances as an alternative criterion when the first was not available, e.g. luteinized unruptured follicle; (iii) follicular rupture: abrupt disappearance or a reduction in size of at least 50% of the echo-image; (iv) ovulation: follicular rupture followed by plasma progesterone concentrations >12 nmol/l in at least two samples taken during the luteal phase; (v) enlarged follicle: follicle with a mean diameter >25 mm; luteinized unruptured follicle: persistent echo-image of a follicle, associated with increased plasma progesterone concentrations; biphasic cycle: cycle in which plasma progesterone concentrations were >12 nmol/l in at least two samples, otherwise it was monophasic; cycle with uncertain endocrine profile: menstrual cycle partially monitored in which it was not possible to assess the occurrence of a luteal phase, e.g. a prolonged follicular phase which ran through the 30 day assessment period.

Statistical analysis

The proportion of women who exhibited ovulation or biphasic cycles at each assessment period was analysed by logistic regression (Hosmer and Lemeshow, 1989). An analysis of variance was used to compare the length of the cycles. The paired *t*-test was used to compare the maximum plasma hormone concentrations (oestradiol and progesterone) and the number of days with a cervical mucus score $\geqslant 10$ between periods with and without luteal activity. The proportion of cycles with and without luteal activity that had endometrial thickness $\geqslant 18$ mm was compared using Fisher's exact probability test.

Results

Ovarian function

Control cycles were biphasic in 21 women and ovulatory in 20 women. The subject who did not ovulate had a luteinized unruptured follicle which was not considered to be a reason for exclusion from the analysis.

During treatment, 60 treated months were assessed. Of the 21 women, 14 ovulated at least once during treatment. Four women ovulated in each of the 3 months assessed, three women in two and seven women in only one of them. The other seven women were anovulatory at each assessment period. The distribution of ovulatory cycles throughout the months of treatment is shown in Figure 1. The proportion of ovulatory cycles was highest during month 1 and decreased progressively with treatment. Using a logistic regression analysis the statistical significance was borderline ($P = 0.06$). However the odds ratio (slope) between months 1 and 5 of treatment was 3.7, which was significant.

According to the hormonal pattern there were 36 biphasic

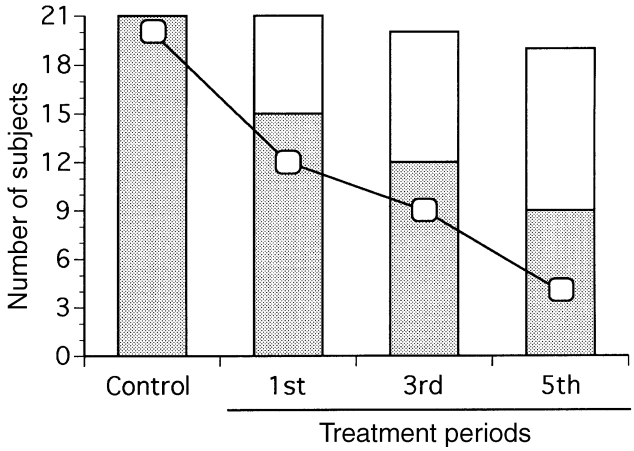

Figure 1. Ovarian function during treatment with 1 mg/day mifepristone for 5 months. Each bar represents the number of subjects with biphasic (shaded bars) and monophasic cycles (open bars) during the control cycle and during months 1, 3 and 5 of treatment. Open symbols represent the number of ovulatory cycles observed in each period.

and 24 monophasic periods. The proportion of biphasic cycles tended to decrease during treatment (Figure 1). Using a logistic regression analysis this tendency was not found to be statistically significant. Ovulation was confirmed echographically in 25 of the 36 biphasic periods. Another six of the biphasic periods corresponded to luteinized unruptured follicles. The five remaining biphasic periods had luteal activity but the critical part of the follicular phase fell outside the assessment period, therefore the occurrence of follicular rupture could be neither confirmed nor excluded. The length of the luteal phase and maximum progesterone concentrations in the ovulatory cycles and in those with unruptured follicles were not significantly different from those observed in the control cycles (data not shown).

An enlarged follicle was found in 13 of the 60 (22%) assessment periods [mean ± SE, 31.5 ± 1.2 mm in diameter (range 27–40)]. In 10 women it was an isolated finding, but in one woman an enlarged follicle was found at each assessment. Follicular enlargement was associated with high oestradiol concentrations (1500–2500 pmol/l) in the three instances in this subject and once in another case. Excluding these two subjects, maximal plasma oestrogen concentrations observed during the periods without luteal activity (mean ± SE, 528.0 ± 57.9 pmol/l) were lower than in those with luteal activity (748.0 ± 55.6 pmol/l) ($P < 0.001$).

Cycle length and bleeding pattern

In all, 21 women recorded their bleeding and spotting episodes during a total aggregate of 101 months of treatment. Their bleeding records show the occurrence of 77 interbleeding periods.

A regular bleeding pattern (range 22–38 days) was observed throughout treatment in nine of the 21 women, allowing the identification of five cycles in each of seven women, six cycles in another and two cycles in one woman who was treated for only 60 days (Figure 2A). In these women the first three treated cycles were slightly longer than the control cycle

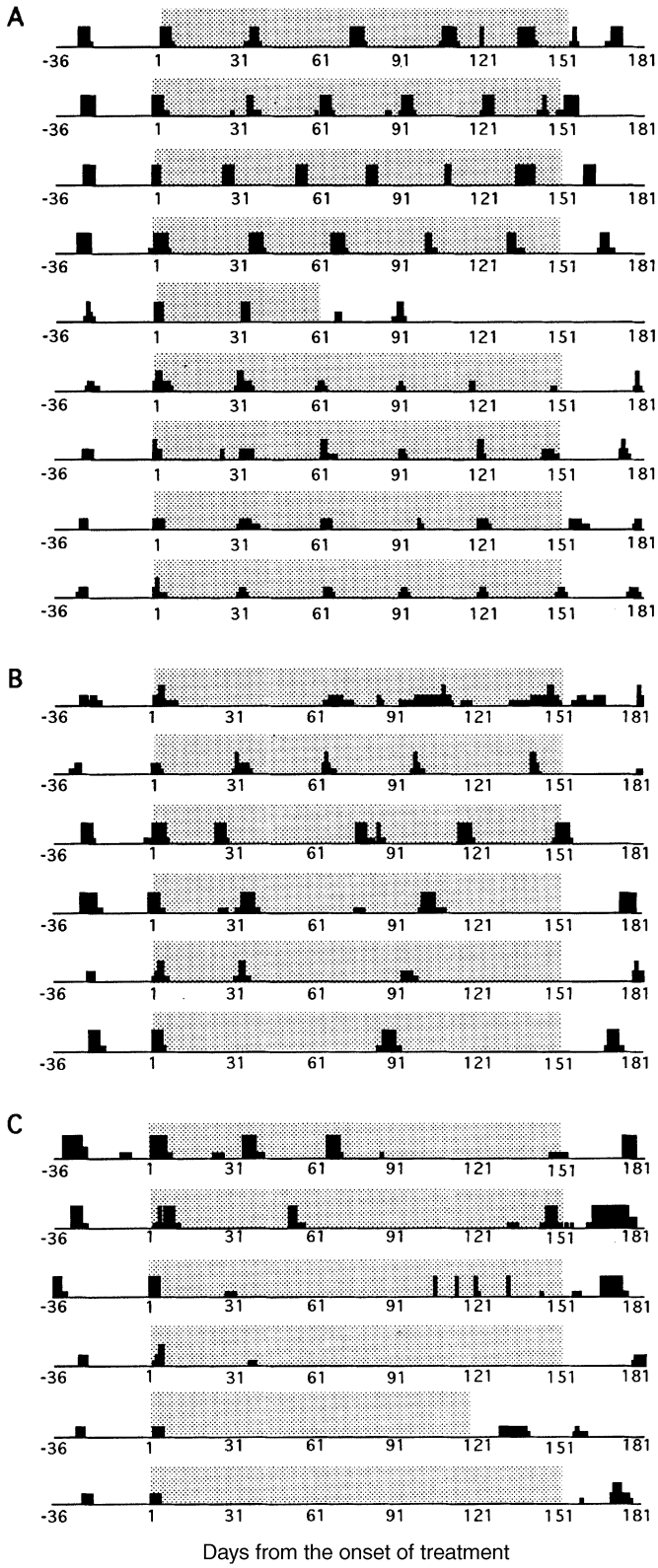

Figure 2. Bleeding pattern during 5 months of treatment with 1 mg/day mifepristone. (**A**) Subjects with a regular bleeding pattern during all treatment. (**B**) Subjects with an irregular bleeding pattern and (**C**) subjects with amenorrhoea. Black areas represent bleeding episodes. The height of the black bars indicates the daily amount of bleeding (small, spotting; medium, normal; large, heavy). Shaded areas represent the period of treatment.

[mean ± SE, 27.0 ± 0.6, 31.3 ± 1.0, 31.0 ± 1.2 and 30.9 ± 1.3 days ($P < 0.02$) for the control cycle and the first three treatment cycles respectively]. The length of the last two treated cycles (27.8 ± 0.9 and 29.9 ± 1.3 days) was not different from the control.

An irregular bleeding pattern, with cycle lengths ranging from 22 to 84 days, was found in six women (Figure 2B), and amenorrhoea during the entire treatment or a segment of it was observed in a further six women (Figure 2C).

Out of 42 cycles within the range of 22–38 days, 31 were biphasic, seven were monophasic and in four the endocrine profile was uncertain. In contrast, of the 12 cycles within the range of 38–90 days, four were biphasic (44, 62, 52 and 83 days), five were monophasic and three were uncertain. Amenorrhoea occurred in six women. In four women the period of amenorrhoea was monophasic, in one the endocrine profile was uncertain and in another, who had amenorrhoea for 129 days, there was a progesterone rise between days 25 and 37 (similar to that of a normal luteal phase but no bleeding was observed when progesterone concentrations fell).

Effects on endometrial development

In the control cycles 21 biopsies were taken, one of which was insufficient for an analysis. A secretory endometrium with a dating according to the LH peak was found in only 13 of the 20 samples. Another five samples corresponded to secretory irregular endometrium, associated in three cases with abnormal findings: one of them with dilated glands, another with tubal metaplasia and the third with epithelial glandular metaplasia. Signs of metaplasia were not observed during treatment in these women. Another two samples corresponded to involuted endometrium, one taken on day +11 of the luteal phase and the other during an insufficient luteal phase.

During treatment 56 biopsies were taken, three of which were insufficient for analysis. Secretory signs were observed in 39 biopsies, nine were proliferative and five were involuted. Among the 39 samples with secretory signs, only one taken during the first month of treatment, on day 9 after ovulation, had an endometrial dating in agreement with the timing of ovulation; all others corresponded to irregular, delayed or mixed endometrium.

In all, 20 of the samples exhibiting secretory signs were obtained during the follicular phase, and the remaining 19 were taken during the luteal phase. All samples showing proliferative endometrium were taken in the follicular phase, whereas involuted endometrium was found in both phases.

Among the samples taken during the luteal phase, 15 were removed on days 7–10 of the luteal phase, with progesterone concentrations within the range 20–75 nmol/l; these are listed individually in Table I.

Table II summarizes the results of the endometrial assessment performed during treatment in the subgroup of women who had normal endometrium during the control cycle. Only one of the 29 biopsies, not classified as proliferative, exhibited normal development. In the subgroup of women who had an abnormal endometrium during the control cycle, the alterations of the endometrium found in the control cycles did not worsen during treatment. On the other hand, the alterations found in samples taken during treatment in these subjects were not different from those found in the normal subgroup.

Dilated endometrial glands were observed in 18 of the 53 samples taken during treatment. Of these, 11 samples were taken during cycles longer than 39 days and the other seven during cycles within the normal length, five of which were ovulatory.

The range in value of maximal endometrial thickness observed in 21 control cycles was 6–16 mm. Values ranging from 18 to 28 mm were observed in nine of the 60 assessment periods during treatment. Maximal endometrial thickness was increased to ⩾18 mm during treatment in six of the 19 subjects who completed the study: this was detected only in treatment months 1, 3 or 5 in three subjects, in months 1 and 5 in one subject and in months 3 and 5 in two subjects. Thus the longer the duration of treatment, the greater the chance of encountering increased endometrial thickness. Two instances of increased maximal endometrial thickness were observed during 36 treatment cycles with luteal activity. In contrast, maximal endometrial thickness was increased to ⩾18 mm in seven of 24 cycles (29%) with no luteal activity ($P = 0.023$; Table III). This increased thickness was associated with amenorrhoea in one woman (28 mm). The women in four of the seven instances also had dilated endometrial glands. Maximal plasma oestradiol concentrations in these seven cycles were not increased and remained within the range 310–660 pmol/l. All increases in maximal endometrial thickness took place in women who had a normal endometrial morphology in their control cycle. Six of the seven increases in endometrial thickness to ⩾20 mm were observed in women whose maximal thickness in the control cycle was in the upper end of the range (14–16 mm).

Effects on cervical mucus score

Treatment had no significant effect on cervical mucus score (CMS) except for an increase in the number of days with a CMS ⩾10 in periods with no luteal activity compared with periods with luteal activity ($P = 0.03$). During the control cycle the 11 subjects sampled had luteal activity; their CMS were ⩾10 for 0–2 days. During the first month of treatment the CMS was ⩾10 for 2 and 5 days respectively in two subjects who had no luteal activity; the CMS was ⩾10 for 0–3 days in the nine women who had biphasic cycles. During the fifth month of treatment, nine women were evaluated. The number of days with a CMS ⩾10 was in the range 0–9 in those with no luteal activity ($n = 5$) and 1–3 in those with biphasic cycles ($n = 4$), with a median of 4.0 and 2.5 days respectively.

Side-effects

No untoward reactions were reported by the volunteers. Clinical chemistry, blood cell counts and urine analyses were performed at enrolment and at the end of the third and fifth treatment periods. The chemical analysis included measurement of serum glutamic oxalacetic and pyruvic transaminase, lactic dehydrogenase, alkaline phosphatase, bilirubin, total protein, cholesterol, uric acid, urea nitrogen, glucose, inorganic phosphate and calcium. All were within the normal range.

Table I. Endometrial morphology on days 7–10 of the luteal phase during continuous treatment with 1 mg/day mifepristone

Subject no.	Treatment month	Day of luteal phase	Endometrial morphology (dating)	Progesterone[a] (nmol/l)
15	1	+9	Secretory normal (day 22)	55.0
16	1	+7+8	Secretory irregular	53.5
17	1	+7	Secretory irregular	35.2
18	1	+8+9	Secretory delayed (day 17)	54.8
19	1	+8+9	Secretory delayed (day 17)	75.0
21	1	+8+9	Secretory delayed (day 17)	31.7
12	3	+9	Secretory irregular	30.6
15	3	+9	Mixed	36.7
16	3	+7	Secretory delayed (day 17)	56.5
19	3	+9	Secretory irregular	75.0
21	3	+8+10	Secretory delayed (day 17)	NM
9	5	+8	Secretory delayed (day 17)	19.6
15	5	+10	Secretory delayed (day 18)	67.6
19	5	+8+9	Secretory irregular	75.0
21	5	+8+10	Secretory delayed (day 17)	37.0

NM = not measured.
[a]Progesterone concentrations on the day of endometrial biopsy.

Table II. Endometrial morphology during continuous treatment with 1 mg/day mifepristone in subjects who had normal endometrium before treatment

	n[a]
Proliferative	6[b] (2)
Secretory normal	1
Secretory irregular or delayed	18 (5)
Mixed	7 (4)
Involuted	3 (2)

Values in parentheses are the number of samples that presented dilated glands.
[a]In all, 13 subjects contributed three biopsies each. The four missing biopsies correspond to insufficient sample ($n = 1$) and biopsies not taken in the third and fifth treatment month.
[b]Endometrial biopsies taken before the progesterone rise.

Table III. Maximal endometrial thickness according to luteal activity during continuous treatment with 1 mg/day mifepristone

Periods	Luteal activity[a] mm [mean ± SD (*n*)][b] [outlying values][c]	No luteal activity mm [mean ± SD (*n*)] [outlying values]
Control	11.7 ± 2.9 (21)	
Treatment		
Month 1	11.2 ± 2.3 (14) [22]	9.6 ± 1.9 (6)
Month 3	11.2 ± 2.7 (11) [19]	12.7 ± 1.8 (6) [20,22]
Month 5	12.3 ± 1.7 (9)	12.4 ± 4.1 (5) [18,20,24,27,28]

[a]Plasma progesterone concentrations >12 nmol/l in at least two consecutive samples taken 1 or 2 days apart.
[b]Outlying values >16 mm were excluded from the calculation of mean ± SD (*n*).
[c]Proportion of outlying values in periods with versus without luteal activity ($P = 0.023$).

Discussion

Mifepristone given continuously at a dose of 1 mg/day disrupted endometrial development in all subjects during treatment. Only one of the 53 samples exhibited a secretory endometrium in phase with the hormonal events, and this occurred in the first treatment cycle. However, 40% of the cycles were monophasic, and bleeding cyclicity was altered in 57% of cases—a much larger proportion than desirable. These results suggest that a lower dose might still affect endometrial maturation without altering ovarian sex hormone secretion. Recently Gemzell-Danielsson *et al.* (1997) reported that the continuous daily administration of 0.5 mg/day mifepristone for 3 months did not alter follicular growth, oestrone glucuronide, pregnanediol glucuronide, LH concentrations in urine or cycle length, and that all five subjects ovulated during treatment. At the same time endometrial development appeared to be slightly retarded and exhibited decreased binding of *Dolichos biflorus* agglutinin and decreased glycodelin expression. A dose of 0.1 mg/day had no significant effect on the endometrium. It remains to be seen to what extent the endometrial effects of 0.5 mg/day mifepristone exert a contraceptive effect.

The study of Gemzell-Danielsson *et al.* (1997) and our study do not resolve the question of the feasibility of endometrial contraception using a continuous low-dose antiprogestin but provide a fair basis to select a dose for a phase 2 clinical trial and also a basis for comparison between different antiprogestins in future studies. An alternative regimen for endometrial contraception, which appears to be particularly suitable for mifepristone in view of its long half-life in the circulation (Deraedt *et al.*, 1985; Kekkonen *et al.*, 1996), is the intermittent or once a week administration reported by Gemzell-Danielsson *et al.* (1996). The once-weekly administration of 5.0 or 2.5 mg delayed endometrial development and impaired secretory activity without inhibiting ovulation. The closest proof of the feasibility of endometrial contraception so far has been the single administration of 200 mg mifepristone in the early luteal phase (Gemzell-Danielsson *et al.*, 1993). When the contraceptive efficacy of this regimen was tested in 21 unprotected women in a total of 157 ovulatory cycles, only one clinical pregnancy occurred.

Another important issue concerned with the use of con-

tinuous low-dose antiprogestins for endometrial contraception is safety. It has been feared that the administration of antiprogestin for prolonged periods of time will expose the endometrium to continuous oestrogen action not antagonized by progesterone, and that this could be unsafe for women. In this study the only endometrial alterations found that relate to this concern were increased endometrial thickness and dilated endometrial glands. Six of the 19 subjects who completed the study, who had increased endometrial thickness up to ⩾18 mm, represented the affected group. Although the numbers were too small to draw any conclusions, there was a tendency to encounter these effects more frequently in the later than in the earlier assessment periods. Similarly, the largest increases in endometrial thickness (24, 27 and 28 mm) were only observed in the fifth month of treatment. Another important feature was that thickening was significantly more likely to occur in assessment periods with no luteal activity. Because most of the increases were associated with neither amenorrhoea nor elevated oestradiol concentrations, they cannot be explained by stronger or longer oestrogenic stimulation. It is more likely that unopposed oestrogen stimulation acting on predisposed individuals is responsible for greater endometrial growth. This is difficult to prove, but the fact that subjects who had a thicker endometrium in the control cycle were more likely to have increased endometrial thickness during treatment suggests that this may be the case.

The finding of dilated glands in endometrial samples taken during treatment is in contrast to the significant decrease in the diameter of glands reported during the second month of treatment with 5 mg mifepristone administered once a week (Gemzell-Danielsson *et al.*, 1996) and during the third month of treatment with 0.5 mg/day mifepristone (Gemzell-Danielsson *et al.*, 1997). The different endometrial response observed in our study does not have an obvious explanation. In the studies of Gemzell-Danielsson *et al.* (1996, 1997), mean glandular diameter was calculated from morphometric assessment. In our study the labelling of a sample with dilated glands resulted from the visual assessment performed by the pathologist at low magnification; however, this methodological difference is unlikely to explain contradictory findings. In the study with 5 mg/week mifepristone, it is likely that partial suppression of oestradiol concentrations may have occurred. In addition, this dose may have a qualitatively different effect on the endometrium. In the study with 0.5 mg/day mifepristone only five women were studied, and this low number, combined with low incidence of the event, may have eliminated the chance of observing samples with dilated glands. The significance of this type of gland is not evident from these data because no signs of endometrial hyperplasia were observed.

The fact that secretory signs were observed in the endometrium of women with preserved ovarian endocrine function, despite the antiprogestin treatment, could be interpreted as incomplete blockade of progesterone action by the dose used. However, the same secretory signs were also observed in biopsies taken in periods with no luteal activity. Because it has been reported that mifepristone can have agonistic effects on the endometrium, in particular under conditions in which endogenous progesterone is present at low concentrations (Gravanis *et al.*, 1985), this may also be the case for these samples.

The results of this study confirm that endometrial maturation can be affected by the daily administration of low doses of mifepristone without necessarily altering ovarian sex hormone secretion. Whether or not those endometrial alterations will be sufficient to prevent implantation remains to be established.

A tendency for progressive effects over 5 months of treatment was detected at both the ovarian and endometrial level. Its significance is unclear, but it is advisable that this type of phase 1 study is conducted over extended periods of continuous drug exposure.

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