A novel estrogen-free oral contraceptive pill for women: multicentre, double-blind, randomized controlled trial of mifepristone and progestogen-only pill (levonorgestrel)


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BACKGROUND: The acceptability and continuation rate of oral contraceptive steroids are limited by unpredictable bleeding and the fear of long-term risks such as breast cancer. By inhibiting ovulation and by altering the receptivity of the endometrium, antagonists of progesterone, such as mifepristone, could be developed as estrogen-free novel contraceptives. METHODS: Multicentre, double-blind, randomized controlled trial comparing frequency of amenorrhoea (primary outcome), bleeding patterns, side effects and efficacy in women taking daily 5 mg mifepristone (n = 73) or 0.03 mg levonorgestrel (progestogen-only pill; POP, n = 23) for 24 weeks. RESULTS: More women were amenorrhoeic while taking mifepristone than POP (49 versus 0% P<0.001), and fewer women bled or spotted for >5 days per month (4 versus 39% P<0.001). Forty-eight percent of women who took mifepristone for 6 months had cystic glandular dilatation of the endometrium but none showed hyperplasia or atypia. There were no pregnancies in 356 months of exposure in women who used only mifepristone for contraception. Two pregnancies occurred in women taking mifepristone who were also using condoms for dual protection. CONCLUSIONS: Daily mifepristone (5 mg) is an effective oral contraceptive pill which has a better pattern of menstrual bleeding than an existing POP (levonorgestrel).

Keywords: antiprogestins; contraception; levonorgestrel; mifepristone; progestogen-only pill

Introduction

Fifty years have passed since the first clinical trials in Puerto Rico demonstrated that a daily pill containing ethinyl estradiol and norethynodrel was a highly effective contraceptive (Pincus et al., 1958). Contraceptive development since the introduction of the pill has been limited to variations on the theme of steroid hormones [new delivery systems, different progestogens, lower doses of estrogen (Baird and Glasier, 1999; Population Reports, 2003)]. Oral contraceptives, containing either progestogen or a combination of estrogen with progestogen, are popular because they are highly effective and easy to use (Baird and Glasier, 1999; Population Reports, 2003). However, continuation rates are often disappointingly low.

The commonest reason for discontinuation of combined oral contraception (COC) is breakthrough bleeding (Rosenberg and Waugh, 1998) but fear of breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer, 1995; Larsson et al., 1997; Althius et al., 2002), and to a lesser extent venous thromboembolism, are significant disincentives to both uptake and continuation despite the obvious convenience of relief of dysmenorrhoea and other symptoms related to menstruation (ESHRE Capri Workshop Group, 2005). Progestogen-only pills (POP) have the advantage of fewer serious risks but are associated with unpredictable vaginal bleeding which is the commonest reason for discontinuation (McCann and Potter, 1994; Fraser, 1999). In many surveys,
fewer than 50% of women continue using oral contraceptives for > 12 months (D'Arcangues et al., 1992).

Even the regular pattern of monthly bleeding characteristic of the combined pill is considered undesirable by some women. When oral contraceptives were first marketed it was assumed that women would prefer to have a monthly cycle because it would be perceived as more ‘natural’ (Pincus 1965). Recently, it has been shown that many women, regardless of age, prefer to have either predictable bleeding less often than once a month or not to bleed at all (Den Tonkelaar and Oddens, 1999; Glasier et al., 2003).

Mifepristone is a synthetic C19 steroid which is a potent antagonist of progesterone (Ullmann, 2000). There is very little information about the use of mifepristone (or other progesterone receptor modulators) for contraception in spite of the fact that the original clinical publication 23 years ago demonstrated its contraceptive as well as abortifacient properties (Herrman et al., 1982; Baird, 2001). The lack of progress with these compounds has not been due to scientific reasons but relates to the political and religious controversy surrounding RU486 (‘the Abortion Pill’). In low daily doses, mifepristone has been shown to inhibit ovulation by suppressing the pre-ovulatory surge of LH and acting directly on the endometrium to induce amenorrhoea in the majority of women (Ledger et al., 1992; Croxatto et al., 1993; Cameron et al., 1995; Brown et al., 2002). We have previously demonstrated in a pilot study that mifepristone at a dose of 2 or 5 mg/day has contraceptive potential (Brown et al., 2002). In contrast to pills containing estrogens and/or progesterogens, there is no theoretical risk that such a pill would increase the risk of breast cancer or cardiovascular disease. Rather, experimental data show that anti-gestogens are antimitotic in breast cancer cell lines and animal models and hence might actually reduce the risk of malignancy (Horowitz, 1992; Klijn et al., 2000; Poole et al., 2006).

A pill which contained no estrogen and which reproducibly induced amenorrhoea in high proportion of women should prove popular. In the present study, therefore, we directly compared the pattern of bleeding and other side effects of mifepristone at a dose of 5 mg/day for 24 weeks with a method of contraception in common use in the UK, the POP (levonorgestrel). We hypothesized that women given mifepristone would have a much higher incidence of amenorrhoea and fewer days of menstrual bleeding.

Materials and Methods

This was a multicentre, double-blind, randomized controlled phase II trial comparing two daily contraceptive pills. The primary outcome was the percentage of women who had amenorrhoea throughout the study. Secondary outcomes included number of days of bleeding, endometrial thickness and histology, and number of pregnancies. Before starting, the trial was approved by the steering committee of the Contraceptive Development Network (MRC Grant No. G9523250). It was performed in accordance with Good Clinical Practice including regular monitoring of centres.

Between June 2003 and January 2004, a total of 97 healthy volunteers with regular menstrual cycles (21–42 days) aged 18–40 years were recruited from four sites (34 in Sagamu, Nigeria; 18 in Cape Town, South Africa; 10 in Hong Kong, People’s Republic of China and 35 in Edinburgh, Scotland). The study was approved by local ethical committees at all centres. All women gave written informed consent before enrolment and were screened before entering the study by routine physical and gynaecological examination and measurement of height, weight, blood pressure and pulse rate. Blood samples were collected for measurement of progesterone, clinical chemistry and haematology. The size of the uterine cavity and ovarian follicles were measured by transvaginal ultrasound scan. Urinary hCG was also measured to exclude pregnancy before entering the trial. Women who had used any form of hormonal contraception within the last 3 months of the start of the study were excluded except in Edinburgh where nine women with regular cycles while already using a POP were included without having to undergo a washout period.

Subjects were studied for one pretreatment cycle, six treatment cycles (24 weeks) and for one post-treatment cycle. Subjects were randomly allocated to receive either mifepristone 5 mg/day (one half a 10 mg tablet) (from Laboratoire Exelgyn, 6 rue Christophe Colomb, 75 008-Paris for women in Edinburgh; and from Hualian Pharmaceuticals Ltd, Shanghai, China for women in Shanghai, Cape Town and Sagamu) or levonorgestrel 0.03 mg/day (POP) (Norgeston; Schering Health Care Limited, The Brow, Burgess Hill, West Sussex, RH15 9NE) starting on Day 1 or 2 of the cycle. Randomization was achieved by blocked computer-generated randomization performed individually for each centre to ensure good balance of numbers in the different treatment groups. Each centre was given numerical sequence of coded treatment bottles which were identical generated by statistician in Edinburgh office. Participants were enrolled in each centre by the local investigator. The numerical sequence was determined by the clinical trials manager in Edinburgh. To maximize, the number of cycles observed on mifepristone without greatly reducing the power of the randomized comparison, three times as many subjects were randomized to mifepristone as to levonorgestrel. In Cape Town, Hong Kong and Edinburgh, daily doses were issued at eight weekly intervals in pre-packed identical bottles containing mifepristone (a half tablet) with placebo, or levonorgestrel with one half placebo tablet. In Nigeria, daily doses were issued at weekly intervals. The placebo and active tablets were both white but of slightly different size. Unused medication was returned and new medication dispensed at this time. All subjects were sexually active and intending to use the study drug as their sole method of contraception. However, in Cape Town and Hong Kong some women also used condoms for protection against sexually transmitted infection. Cycles in which dual protection was used were omitted when calculating the months of exposure to the risk of pregnancy.

The women were asked to record every day the amount of vaginal bleeding and adverse events on a diary card. If bleeding occurred it was recorded as spotting (one or less pad/tampon required) or bleeding (more than one pad/tampon required).

Subjects attended the clinic for review at eight weekly intervals during the treatment phase and once more on Day 5–11 of the first menstrual cycle after discontinuation of the study medication. At the end of the treatment phase a vaginal examination was performed on all subjects and an endometrial biopsy performed in a subgroup of volunteers. In order to identify those women who might develop hyperplasia of the endometrium a biopsy was performed at any time during the study on all subjects if the measurement of the uterine cavity was observed to be >12 mm (‘safety biopsy’). Biopsies were performed as an outpatient procedure with a Pipelle suction curette (Pipelle de Cornier, Laboratoire C.C.D, 60 rue Pierre Charron, 75 008-Paris-France, Ref. 1103000). Endometrial samples were then fixed in 10% neutral buffered formalin prior to embedding in paraffin wax. Histological examination of the endometrial sections was
conducted blind by an independent pathologist and classified into five categories [proliferative, secretory, inactive, insufficient and cystic glandular dilatation (CGD) as previously described (Baird et al., 2003)]. (i) Proliferative includes ‘active’ in which glands are tubular, with columnar epithelial cells showing nuclear stratification and frequent mitoses (>5 per 20 gland profiles); and ‘weakly’—simple tubular glands with columnar epithelial cells showing mild nuclear stratification (2–4 mitoses per 20 gland profiles). (ii) Inactive—cuboidal to columnar cells showing focal or diffuse nuclear stratification, in glands with simple tubular or undulating profiles without significant dilatation. Resembles endometrium of basalis in normal cycling endometrium. Glands are not atrophic, and show evidence of limited recent growth or function, but lack the findings seen in normal cycling proliferative endometrium. Mitoses are absent or uncommon (no more than om mitotic figure per 20 gland profiles). (iii) Inactive with CGD—inactive glandular epithelium as described above, with dilatation of gland lumina. Dilatation is defined as the gland having an open lumen that forms a space, i.e. greater than four times the epithelial thickness. (iv) Secretory—glands are variably tortuous with cytoplasmic vacuolation that varies according to phase of cycle. Cells are columnar, with non-stratified nuclei showing an absence of mitoses (except for infrequent mitoses in the early secretory phase). Stromal decidual change starts around spiral vessels, becoming confluent in the late secretory phase. Some samples contained inadequate amounts of tissue for accurate histological evaluation.

Ovarian function was assessed by the measurement of progesterone in venous blood collected at screening and at 8, 16 and 24 weeks after starting treatment. The woman was classified as having ovulated at any time if the concentration was >15 nMol/l in any of the three samples. Following centrifugation the serum was stored at −20°C in labelled sample tubes. Analysis by radioimmunoassay was carried out at the end of the study locally by each centre. Transvaginal ultrasoundography was used to assess number and size of follicles or cysts at screening and after 8, 16 and 24 weeks.

Statistical methods
The number of subjects on mifepristone was chosen to give an upper confidence limit of <5% for the risk of pregnancy over the 6 months of treatment if no pregnancies occurred in that group. To maximize, the number of cycles observed on mifepristone without greatly reducing the power of the randomized comparison, three times as many subjects were randomized to mifepristone as to levonorgestrel. These numbers were also sufficient to give over 99% power to show a significant difference in the rate of amenorrhoea over 6 months if the rate was 50% on mifepristone when compared with the 5% anticipated in the levonorgestrel group (Collaborative Study Group, 1998).

Data analysis was carried out using SPSS version 12 (SPSS, Inc., Chicago, IL, USA) and Excel 2003 (Microsoft Corporation). The two randomized groups were compared by chi-squared test with Yates’ correction and Mann–Whitney or Student’s t-tests as appropriate tests for binary and continuous outcomes, respectively. Analysis of covariance adjusting for pretreatment values was used to compare the endometrial thickness in the two groups at follow-up. Confidence limits were calculated for the incidence efficacy outcomes in the mifepristone group using the Poisson distribution based on person time at risk.

Results
A total of 97 women were recruited (Fig. 1) and randomized to treatment [35 in Edinburgh (26M, 9POP); 34 in Nigeria (26M, 8POP); 18 in Cape Town (14M, 4POP); 10 in Hong Kong (8M, 2POP)]. One subject randomized to mifepristone withdrew for personal reasons and discarded the study drugs without taking any. Therefore, the results of the 96 women who started treatment [73 received mifepristone (M), 23 received levonorgestrel (POP)] were included for analysis.

Of the 87 women who started the study and did not use hormonal contraception in the previous months, 66 were randomized to mifepristone and 21 to POP. An additional nine women in Edinburgh who had regular menstrual cycles while taking POP for contraception were transferred directly to study medication. In this subgroup, seven were randomized to mifepristone and two to POP.

When all centres were combined (Table 1) there were no statistically significant differences in age, weight, height, BMI or parity between the two treatment groups (two-sample Student’s t-tests). However, there were some differences in the characteristics of the women from different centres. The women in Nigeria were significantly older (years 33.9 ± 4.2 SD, P = 0.001) than the women in both Cape Town (26.2 ± 7.7) and Edinburgh (28.7 ± 6.0). The BMI of women in Hong Kong (19.8 ± 1.7 kg/m²) was significantly lower than that of women in Edinburgh (22.9 ± 1.9, P < 0.001), Nigeria

Table 1: Mean (SD) age, weight, height and BMI according to study drug

<table>
<thead>
<tr>
<th></th>
<th>M</th>
<th>POP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.3 (6.3)</td>
<td>30.4 (6.9)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>60.7 (9.1)</td>
<td>58.4 (6.2)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161.5 (5.9)</td>
<td>161.3 (6.3)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.3 (3.6)</td>
<td>22.4 (1.8)</td>
</tr>
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on 22 January 2018

Menstrual bleeding pattern

There were significant differences in the pattern of menstrual bleeding between the groups (Fig. 2). Of the 73 women who started mifepristone, 36 (49%) were amenorrheic for the duration of drug treatment and only three women bled or spotted on average for five or more days per month. In contrast, none of the women in the POP group were amenorrheic. Although episodes of bleeding in the women who took mifepristone were infrequent and slight, they were mostly unpredictable, except in Nigeria where 4 of the 15 women who continued to bleed had regular monthly periods. Nigerian women were more likely to experience bleeding over the 6 month study duration (13/21; 62%) than those from other centres [Edinburgh 4/22 (18%); Cape Town 3/9 (33%); Hong Kong 1/6 (17%)]. There was a significant difference in bleeding frequency between Nigeria and Edinburgh (χ² = 6.86; P = 0.009).

Ovarian function

Ovarian function was assessed at baseline, 8, 16 and 24 weeks after starting treatment by measurement of progesterone in blood. In 33 of the 97 pretreatment samples, the concentration of progesterone was >15 nmol/l indicating that in just over a third of the women the blood was collected in the luteal phase after ovulation. At each eight-week review, there was evidence of ovulation in some women in both groups. If a woman showed evidence of ovulation at any of the three review visits she was classified as ovulatory. Ovulation was less likely to occur in women taking mifepristone (14/73; 19%) than in those in the POP group although there was no statistically significant difference (7/23, 30%; χ² = 0.72; P = 0.40). However, there were significant differences between centres in the incidence of ovulation and amenorrhea. For example, while taking mifepristone only one of the 26 women in Edinburgh (4%) ovulated when compared with 11/26 women in Nigeria (42%; χ² = 8.78; P = 0.003). The proportion of women who ovulated while taking the POP was identical in the two centres (37%).

Ultrasound examination revealed the presence of numerous small and medium-sized follicles in the ovaries of women in both groups throughout treatment. Follicular cysts (diameter

Table 2: Distribution of mean (SD) numbers of days bleeding and/or spotting while on drug according to treatment group, in the 72 women who took the treatment for at least 6 months (%)

<table>
<thead>
<tr>
<th>Number of days</th>
<th>Bleeding/spotting</th>
<th>Bleeding only</th>
<th>Spotting only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>POP</td>
<td>M</td>
</tr>
<tr>
<td>0</td>
<td>25 (44)</td>
<td>0 (0)</td>
<td>36 (63)</td>
</tr>
<tr>
<td>1</td>
<td>4 (7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2.5</td>
<td>8 (14)</td>
<td>2 (13)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>6–10</td>
<td>10 (18)</td>
<td>1 (7)</td>
<td>7 (12)</td>
</tr>
<tr>
<td>11–20</td>
<td>5 (9)</td>
<td>3 (20)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>21+</td>
<td>6 (11)</td>
<td>9 (60)</td>
<td>5 (9)</td>
</tr>
</tbody>
</table>

(24.3 ± 3.9, P = 0.001) and Cape Town (23.1 ± 3.6, P = 0.014).

Twenty-four women (16M, 8POP) did not complete the full 24 weeks of treatment. Eight women withdrew for personal reasons unrelated to the study medication (e.g. moved from the area, relationship ended); six were discontinued by the investigators because of persistent protocol violations (e.g. poor compliance, unavailable for follow-up). Two women withdrew because of anxiety about potential adverse effects of the pills. Four women in the POP group discontinued because of persistent irregular bleeding, no women in the mifepristone group discontinued for this reason (P < 0.01). Four women withdrew because of pregnancy: three in the mifepristone group and one while using levonorgestrel.

Seventy-two women completed the study (57M, 15POP) and took the medication for at least 24 weeks (168–192 days).
> 30 mm) were detected on eight occasions (six among women using mifepristone and two in the POP group). The cysts were asymptomatic and resolved spontaneously by the next examination without treatment.

**Endometrial thickness**

In the mifepristone group, the width of the cavity and the thickness of the endometrium increased with time relative to the baseline (Table 3). In contrast, there was no statistically significant change in the POP group, and by 16 weeks the difference in the size of the uterine cavity between the groups was statistically significant (P = 0.043). There were differences between the centres in the extent of the increase in size with the thickest endometrium at 24 weeks occurring in Edinburgh (5.2 ± 2.1 mm before starting, increasing to 13.8 ± 7.1 at 24 weeks) (Table 4).

**Endometrial biopsies**

A total of 39 women had at least one endometrial biopsy. Six women in the mifepristone group had two biopsies and one had three biopsies, making a total of 47 biopsies available for examination. Twenty women (19 in the mifepristone group and 1 in the POP group) had a ‘safety biopsy’ because the endometrial cavity on ultrasound was > 12 mm. A total of 31 biopsies were available from women who had completed 24 weeks of treatment (27 mifepristone and 4 POP).

CGD was found in the endometrium of 13 of the 27 women who had a biopsy at 24 weeks on completion of the study. The remainder were proliferative (4), inactive (3), or insufficient for histological examination (7). Of the 19 women on mifepristone who had a ‘safety’ biopsy because the endometrial cavity was dilated above 12 mm, 11 showed CGD on at least one occasion. CGD also occurred in four of nine women with normal-sized cavity who volunteered to have an endometrial biopsy at 24 weeks. The endometrium in the sole woman in the POP group who had a safety biopsy (cavity 13 mm) was too scanty for histological examination. None of the women in either group showed evidence of hyperplasia or atypia.

Hysteroscopy was performed as an outpatient procedure on two women (both in Edinburgh) with an enlarged uterine cavity (29 and 16 mm) detected on routine ultrasound at 16 weeks. The uterine cavity was dilated with mucous fluid and a pale oedematous looking endometrium which showed CGD on histological examination (Fig. 3). No serious pathology was detected and one woman opted to continue with the trial. The endometrial cavity returned to normal size after completion of the trial.

**Contraceptive efficacy**

Not all the subjects were at risk of pregnancy for the duration of the study. Some women separated from their partner, while a number of women in Cape Town and Hong Kong used barrier methods as well as the study drug for dual protection. In total, there were 356 months of exposure in women who took mifepristone as their sole method of contraception and 85 in women who took POP.

Five women became pregnant during the study: four of them in the group of women randomized to mifepristone. However, there were only three pregnancies while the subjects were taking the study drugs. In the mifepristone group, two pregnancies occurred (both in Cape Town) during treatment and were recognized after 62 and 115 days of treatment, respectively. Conception occurred in both within the first 2 months of treatment. One woman underwent a vacuum aspiration and the other opted to continue with the pregnancy and delivered at term of a healthy baby. Both of these women were using condoms for dual protection. Inclusion of these two women in the analysis of efficacy gives an estimate of 0.6% (95% confidence limits 0.07 to 2.0%) for the risk of pregnancy per month while exclusion results in an estimate of 0% (0 and 1.1%). Two additional pregnancies occurred before starting or several weeks after stopping mifepristone. One pregnancy occurred in a woman using levonorgestrel and was only detected because of a routine pregnancy test 8 weeks after starting treatment. She had a blighted ovum and the uterus was evacuated surgically. There was no significant difference in the pregnancy rates between the groups although the study was not powered to detect differences.

**Adverse effects**

There were no major adverse events in either group. Eight women (35% of those taking POP) and 19 (36% of those on mifepristone) reported a range of symptoms none of which were significantly different between the groups including abdominal discomfort (12% mifepristone versus 4% POP), irregular bleeding (7% mifepristone versus 9% POP), headache (8% mifepristone versus 22% POP), flushes (7% mifepristone versus 0% POP) and mood change (3% mifepristone versus 0% POP).

**Discussion**

This study has demonstrated striking differences in the pattern of menstrual bleeding between women taking two types of oral
contraceptive pills, which contain no estrogen. The results confirm our previous study, which reported that the majority of women taking 5 mg mifepristone every day for four months were amenorrhoeic (Brown et al., 2002). In the present study, over 80% of women who took mifepristone were either amenorrhoeic or had episodes of bleeding or spotting <2 days per month. In comparison, women on levonorgestrel had frequent irregular bleeding (>5 days per month) and none was amenorrhoeic. Four women discontinued the POP because the bleeding pattern was unacceptable.

This study has its strengths and weaknesses. The placebo was similar but not identical to either of the active drugs and hence the study was not truly double blind. It would have been possible for the persistent subject and/or researcher to identify group differences by the size of the treatment tablets. We think that this is unlikely because each woman was supplied with two identical opaque bottles each containing 8 weeks supply of either placebo or active drug prepared by a member of the research team not involved with contact with the subjects. Moreover, the difference in bleeding patterns (the primary end point) was so striking that we think it unlikely that unblinding of an individual subject would have had a significant impact on the overall results.

Nine women (all in Edinburgh) who were taking POP were recruited directly to the study without at least 3 months ‘wash-out’. It could be argued that in these women there was

Figure 3: Appearance of the uterus of subject 135 who took 5 mg mifepristone per day for 24 weeks. The subject remained amenorrhoeic throughout. (a) After 8 weeks the thickness of the endometrium and cavity was normal; (b) at 16 weeks the cavity was dilated to 17 mm with fluid. Cyst like structures had become apparent in the cervix; (c) the cavity was lined by pale dilated endometrium; (d) showing CGD on histology (X10); (e) by 24 weeks the cavity was still dilated; (f) by 4 weeks after stopping the cavity had returned to normal after menses. Note the persistence of dilated cervical glands.
a ‘carry over’ effect on the ovary and/or endometrium from the previous treatment. We think that this is unlikely because all women had regular menstrual bleeding while on the POP. Moreover, at recruitment they had evidence of ovarian activity, i.e. luteal levels of progesterone, follicles >10 mm and/or endometrium >8 mm. Because they were randomized 2:7 POP:mifepristone, they would not bias the comparison between the groups. The seven women in this subgroup who were randomized to mifepristone had amenorrhea for at least 3 months after starting, illustrating one of the clinical uses when the drug becomes available.

There were minor differences between centres in the response to the drug. However, in all centres the bleeding pattern was better with mifepristone and the contraceptive efficacy was high.

It is arguably in Africa where there is the greatest unmet need for contraception. The fact that we show that it is effective in a range of cultures, including Africa, should help facilitate its use worldwide particularly in those cultures where women who are menstruating are subject to social taboos.

In the women in the mifepristone group who continued to bleed there were differences between the centres in the pattern of menses. Nigerian women were more likely to experience bleeding over the 6 months study and to show biochemical evidence of ovulation than women in the other centres. For logistic reasons, our assessment of ovarian function by measurement of the concentration of progesterone every 8 weeks was imprecise. We classified a woman as being ‘ovulatory’ if the level of progesterone was in the luteal phase range on any one of the three occasions when it was collected. We argued that there would be about a one in three chance that the progesterone level will be raised in any single sample collected at random from normal cycling women as was found in the control cycle. Although the majority of women in all centres failed to ovulate while taking mifepristone, there were significant differences in the incidence of anovulation between centres.

These differences between centres are intriguing. We have previously reported that ovulation and menstruation were more easily suppressed by mifepristone in Chinese women in Shanghai than in Caucasians in Edinburgh (Brown et al., 2002). The daily dose of 5 mg mifepristone was chosen because it resulted in amenorrhea in over 90% of women in Edinburgh. We have previously suggested that these differences in response may be due to differences in diet and/or in metabolism of steroids. Alternatively, there could be differences in compliance between centres although there was no evidence from the number of returned pills that the women in Nigeria omitted more pills than those in other centres. Moreover, a large number of tablets would have to be missed before sub-therapeutic levels of mifepristone were reached because of the long half-life of mifepristone (Heikinheimo et al., 2003).

One of the main reasons that women discontinue hormonal contraception is because of menstrual irregularity (D’Arcangues et al., 1992) and this was true of women using the POP in this study. All four women who discontinued the study specifically because of menstrual irregularity were taking POP. The amenorrhea or scanty bleeding associated with mifepristone should be perceived as an advantage by many women (Den Tonkelaar and Oddens, 1999; Glasier et al., 2003).

It has been argued that prolonged amenorrhoea is unnatural and even harmful. Monthly menstruation has however been the norm only for the last 100 years. Prior to that, most women spent their short lives either pregnant or breastfeeding and amenorrhoeic. Absence of periods per se does no harm. If associated with hypo-estrogenism (as in the menopause or during treatment with analogues of gonadotrophin releasing hormone) it is associated with increased risk of osteoporosis and heart disease; if associated with a high dose of progestogen (as during the use of Depo Provera) or prolonged exposure to COC (as in extended pill use) it may be associated with increased risk of breast cancer and heart disease (Collaborative Study Group, 1998). Amenorrhea during mifepristone use is not accompanied by hypo-estrogenism and, as stated earlier the risk of breast cancer may be reduced (Horowitz, 1992; Klijn et al., 2000). A recent paper reported that mifepristone prevented the development of breast cancer in transgenic mice with null mutation of BRCA1/p53 (Poole et al., 2006).

Concern has been expressed that with prolonged intake of antiprogestogens the endometrium would undergo hyperplastic or malignant changes due to continued exposure to unopposed oestrogen (Murphy et al., 1995). However, studies in monkeys with mifepristone and other antigestogens have shown evidence of endometrial atrophy rather than hyperplasia (Van Uem et al., 1989; Ishwad et al., 1993; Neulins et al., 1995; Chwalisz et al., 2000). In keeping with our previous report, the endometrial cavity widened progressively with time in women in Edinburgh, but not in the other centres (Brown et al., 2002). We have previously reported that much of the apparent increase in endometrial thickness is associated with cystic dilation of the endometrial glands and the cavity itself (Baird et al., 2003). A recent paper reported the results of a study in which 40 women with fibromyoma were given 5 or 10 mg mifepristone/day for up to 1 year (Eisinger et al., 2005). Simple hyperplasia of the endometrium without atypia was seen after 6 months only in a minority of women (28%) who took 10 mg but none at 5 mg.

In the present study, the commonest histological picture was of inactive CGD. This CGD was only found in those women taking mifepristone. The cause of this unusual change is unknown. It is unlikely to be due to the effects of unopposed estrogen as it has been demonstrated to occur in women who have profound suppression of ovarian follicular development and where oestrogen levels are low (Brown et al., 2002; Baird et al., 2003). Moreover, it occurs more commonly in those women taking 10 mg mifepristone per day than in those taking 5 mg in whom the secretion of ovarian estradiol is higher (Eisinger et al., 2005).

Novel observations in this study were the hysteroscopy finding of atrophic and/or oedematous endometrium. Hysteroscopy revealed that the apparent thickness of the endometrial cavity as measured on ultrasound reflected dilation of the glands and cavity rather than true hyperplasia of the endometrium. It demonstrates the limitation of using measurements of endometrial thickness by ultrasound alone as a marker of...
endometrial pathology. The cause of this accumulation of fluid and its nature is unknown but similar findings have been reported in rabbits following treatment with mifepristone (Chwalisz et al., 2000). It may be that the mechanism, which normally allows the passage and/or re-absorption of fluid from the endometrial glands and uterus, is obstructed leading to an accumulation of fluid within the uterus.

This study has confirmed that mifepristone is potentially a highly effective contraceptive. Even in Nigeria where there was biochemical evidence of ovulation in 42% of women there were no pregnancies in the mifepristone group. In our previous study, we reported no pregnancies in 50 women who used mifepristone at a dose of 2 or 5 mg/day for 4 months (Brown et al., 2002). The present study extends our contraceptive experience to a total of 556 women cycles. The two pregnancies in women taking mifepristone occurred in women in South Africa who were also using condoms as protection against sexually transmitted disease including, HIV/AIDS. It is possible that these women may have omitted to take their pills every day because they thought that they were protected from the risk of pregnancy by the use of condoms.

In conclusion, the present study demonstrates that mifepristone at a daily dose of 5 mg is a safe and potentially effective contraceptive. The relatively high incidence of amenorrhoea or reduced amount of scanty bleeding is likely to be better accepted by women than the irregular unpredictable menstrual bleeding that occurs in the majority of women taking the POP. The reduction of menstrual blood loss should convey health benefits to women particularly in developing countries where the incidence of anaemia is high. Because of its antagonism of progesterone the risk of breast cancer may be reduced rather than increased as is the case with COCs containing estrogen and progestogens (ESHRE Capri Workshop, 2005). A large multicentre phase III trial is required further to assess contraceptive efficacy and safety, particularly with respect to endometrial cancer.

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