Once a month administration of mifepristone improves bleeding patterns in women using subdermal contraceptive implants releasing levonorgestrel

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It has been suggested that the administration of an anti-progesterone might improve bleeding patterns in women with irregular bleeding while using low-dose progestin-only contraception. We report the findings of a double-blind, randomized, placebo-controlled trial of mifepristone (Sino-implant). 50 mg taken once every 4 weeks in 100 Chinese women (50 subjects and 50 controls) complaining of frequent and irregular bleeding while using a levonorgestrel-releasing subdermal contraceptive implant. In all women, regardless of treatment, the frequency of bleeding decreased significantly over 360 days of observation. Women recorded significantly shorter episodes of bleeding (P < 0.0002) during mifepristone treatment than during the 90 days before treatment started. In contrast, the duration of bleeding episodes fell more gradually in placebo-treated controls. Women using mifepristone were more likely to find treatment acceptable than women receiving a placebo tablet (P < 0.01). Despite concern that anti-progesterogenic effects may jeopardize contraception, there were no pregnancies. This approach may offer a useful strategy to improve continuation rates by alleviating unwanted side-effects until bleeding patterns improve spontaneously with time.

Key words: bleeding/contraception/implants/mifepristone/progestin-only

Introduction

Progestin-only contraceptive implants offer highly effective contraception that is long-acting and does not require compliance for effectiveness. The major side-effect is an irregular pattern of uterine bleeding (Fraser et al., 1998). At the end of 5 years, some 25% of Norplant users will have requested removal of the implants because of a bleeding problem (Sivin et al., 1998). In the People’s Republic of China, levonorgestrel-releasing implants account for only a very small amount of contraceptive use, in Shanghai <1% of women use the Sino-implant (Shanghai Dahua Pharmaceutical Plant, Shanghai, China). In a multicentre study (undertaken in China) of two types of levonorgestrel releasing implants, menstrual disturbance accounted for 90% of the reported side-effects and led to a discontinuation rate of 11% at the end of 1 year (Fang et al., 1998).

Although the mechanisms underlying menstrual disturbance are not completely understood (Fraser et al., 1997; Hickey et al., 1999a,b) a variety of approaches have been tested to reduce irregular bleeding in association with progestin-only contraception and thereby to improve continuation rates (Fraser, 1983). It has been demonstrated that the addition of an anti-progesterone to progestin-only contraception reduces the incidence of unscheduled bleeding in monkeys (Williams et al., 1997). In a small pilot study among women using Norplant®, we have demonstrated that a single dose of mifepristone 200 mg induces changes in endometrial progesterone and oestrogen receptors which are consistent with the functional inhibition of progesterone. There was a suggestion that anti-progesterone treatment might improve bleeding patterns, either by a direct effect on the endometrium or by inducing ovulation (Wang et al., 1997). In an attempt to see whether the monthly administration of a single dose of anti-progesterone might confer a clinically significant improvement in bleeding patterns, we undertook a double-blind randomized trial of once a month administration of mifepristone to women using the Chinese levonorgestrel-releasing implant (Sino-implant).

None of the authors has any vested interests of a commercial nature relevant to this study.

Materials and methods

One hundred women aged 18–40 years were recruited from three family planning clinics on the outskirts of Shanghai. All had been using, for at least 3 months (range 3–43, median 15 months), a contraceptive implant (Sino-implant; Shanghai Dahua Pharmaceutical Plant) comprising two rods, each containing 75 mg levonorgestrel, delivering a total dose of 30 µg/day for 3 years. All women were attending the clinic complaining of frequent vaginal bleeding, defined as a bleeding episode occurring more often than once every 24 days. None was receiving any medication and all were fit and well with no history of any gynaecological disease. Local ethical committee approval was obtained for the study and informed consent was given by all participants.

Women were randomized (50 in each group), using random number tables, in blocks of eight attending each clinic, to receive either 50 mg mifepristone (two tablets of 25 mg each) or two placebo tablets (both placebo and mifepristone were provided by the Shanghai Hualian Pharmaceutical Co. Ltd, Shanghai, PR China). Treatment was administered in a double-blind manner.
All women were instructed to keep a daily diary of bleeding and spotting. Spotting was defined as vaginal blood loss not requiring sanitary protection. After being enrolled in the study, a record of bleeding was kept for 90 days prior to starting treatment. After completion of 90 days of record-keeping, women were instructed to attend the family planning clinic for the first treatment on the third day after the start of a bleeding/spotting episode. After the first treatment women were given a date to return to the clinic once every 28 days for 5 months (a total of six treatments in all). Treatment was always given at the family planning clinic, where pill taking was observed by a doctor after urinary β-human chorionic gonadotrophin (HCG) had been measured to exclude pregnancy. At this visit the bleeding diary was checked. Bleeding diaries were continued for a further 90 days after completion of the last cycle of treatment.

Urinary HCG was measured using a kit (Surestep™ HCG; Applied Biotech Inc., San Diego, CA, USA), the lower level of sensitivity of which was 25 IU/l.

Statistical analysis
Since we had no meaningful data on which to base power calculations the sample size was chosen to give sufficient power to detect as significant a mean difference of 0.6 standard deviations. Menstrual diaries were analysed using the MDS Menstrual Diary Analysis Programme (World Health Organization, Special Program of Research, Development and Research Training in Human Reproduction, Statistics and Data Processing Unit, Version 3.0, 1993) (WHO, 1996).

Bleeding patterns were analysed in blocks of 90 days (reference periods) (Figure 1). For each reference period the number of days of bleeding and spotting, the number of episodes of bleeding and spotting; the mean duration of spotting and bleeding episodes and the number of ‘dry days’ (free of bleeding and spotting) were calculated. Thus reference period 1 includes 90 days before the first treatment (mifepristone or placebo). Reference periods 2 and 3 cover a total of 180 days from the first treatment and together include 6 treatment months and the first 12 days of month 7. Reference period 4 started 39 days after the last treatment and ended 90 days later (Figure 1).

In the final analysis, bleeding and spotting days were combined and the data analysed using the Mann–Whitney U-test.

Results
There were no differences in age (29.5 years for subjects, 30 years for controls) or parity (2.6 for each group) between subjects and controls nor in the mean duration of implant use (15.8 ± 2 months for subjects and 16.5 ± 2 months for controls). All women completed the study and there were no pregnancies.

The effect of treatment on bleeding patterns is shown in Figure 2. There were no statistically significant differences between subjects and controls in any of the parameters assessed during the 90 day period before treatment was started. Women in both groups tended to show a similar decrease in the number of bleeding days (and therefore an increase in the number of dry days) with time (Figure 2A). Women treated with mifepristone bled for a mean of 48 ± 15 days (range 21–88) during the first 90 days, falling to 29 days in reference period 2 (P < 0.0002) with a further decrease to 23 days during reference period 3. Women treated with placebo recorded a mean of 51 ± 15 days (range 27–89) of bleeding in reference period 1, falling to 33 days (P < 0.0002) during reference period 2. By reference period 4 (after treatment), there were no significant differences between subjects and controls in any of the bleeding parameters measured. The mean number of bleeding and spotting episodes also fell with time (Figure 2B), with no significant difference between women treated with mifepristone and controls. The most marked difference between the two groups was in the average duration of bleeding episodes (Figure 2B) which, among the subjects, fell from a mean of 14 days before treatment to 6.5 days after the first 90 days of treatment (P < 0.00001). Among controls, the mean duration of bleeding episodes also fell significantly with time from 15 days during the 90 days before treatment to 11.1 days at the end of the first 90 days of treatment (P = 0.0003) and 8.2 days after the completion of all six treatment cycles. The mean duration of bleeding episodes almost halved for both groups of women when the number during the pre-treatment period was compared with that post-treatment, regardless of whether they had been treated with placebo or mifepristone.

Forty-eight subjects and 49 controls completed the post-
Mifepristone improves levonorgestrel-induced bleeding patterns

**Figure 2.** Mean number of bleeding and dry days (A) and number and duration of bleeding episodes (B) among mifepristone-treated women and controls over the four reference periods (RP).

treatment satisfaction questionnaire. Women treated with mifepristone were more likely to rate their treatment as satisfactory than those who received placebo ($P < 0.01$, Table I).

**Discussion**

In all women using the Sino-implant, bleeding patterns improved during the 360 days of follow-up. The number of bleeding days decreased (and inevitably therefore the number of dry days increased) and both the number and duration of bleeding episodes was reduced to a similar extent regardless of treatment. This tendency for bleeding patterns to improve has been observed with Norplant (Shoupe *et al.*, 1991) and has been attributed to an increase in the frequency of ovulation as concentrations of levonorgestrel delivered by the implant gradually fall. We analysed the number of bleeding and spotting days and number of bleeding episodes (among both subjects and controls and both groups combined), comparing women who had been using the implants for durations of less than the median with those who had been using them for longer than the median duration for the group. While there did appear...
to be a slight improvement (Table II), the differences were not statistically significant, in contrast to the differences seen in response to mifepristone administration. The incidence of side-effects also has been reported to decrease with time among women using the Sino-implant (Fang et al., 1998), although whether this is due to an increase in ovulatory cycles is not known.

The only significant effect of mifepristone treatment was on the average duration of bleeding episodes, which more than halved in length during mifepristone-treated cycles but changed much more gradually in women receiving placebo tablets. The duration of bleeding episodes during mifepristone resembled a ‘normal’ menstrual period. Since ovarian activity was not monitored during the study, it is not possible to determine whether induction of ovulation was the cause of the improvement in bleeding patterns. Further studies, with monitoring of ovarian activity, need to be undertaken.

While these results may seem somewhat disappointing, the women clearly found mifepristone to be of benefit. It hardly needs scientific methodology to confirm that a bleeding episode of shorter duration has to be more acceptable than one that continues for days on end.

Levonorgestrel contraceptive implants act mainly by changing the quality of cervical mucus and inhibiting normal sperm penetration (Croxatto et al., 1987). Abnormal endometrial development will prevent implantation, should fertilization occur. Any intervention designed to improve bleeding patterns which ‘inhibits’ the action of the progestogen might theoretically jeopardize contraception. Reassuringly, no woman conceived during 300 ‘cycles’ of use of mifepristone in combination with the Sino-implant. In the event that administration of an anti-progestogen might reverse the contraceptive effects of the progestogen, mifepristone itself at a dose of 50 mg has both contraceptive and abortifacient effects and the risk of pregnancy may in fact be reduced still further.

The results of this study suggest that the once a month administration of mifepristone may be an effective and acceptable way to ameliorate bleeding irregularities and ‘tide women over’ until bleeding patterns improve with time as a consequence of an increasing frequency of ovulatory cycles. It is possible to achieve a similar effect with the combined oral contraceptive pill (Diaz et al., 1990), but most women find the idea of using two hormonal contraceptives simultaneously hard to understand and many have chosen a long-acting implant because they do not like – or cannot remember – to take a pill every day. Further, and more detailed, studies of the mechanism of action of this regimen are warranted.

Table II. Mean number of bleeding and spotting days and mean number of bleeding episodes per 90 day reference period among women with shorter (less than median) or longer (longer than median) durations of implant use

<table>
<thead>
<tr>
<th>Patient</th>
<th>Duration of implant use</th>
<th>n</th>
<th>Mean number of bleeding/spotting days</th>
<th>Mean number of bleeding episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (median 13.5 months)</td>
<td>More than median</td>
<td>24*</td>
<td>44.0 ± 16</td>
<td>4.1 ± 1</td>
</tr>
<tr>
<td></td>
<td>Less than or equal to median</td>
<td>24*</td>
<td>51.2 ± 14</td>
<td>4.3 ± 1</td>
</tr>
<tr>
<td>Controls (median 15 months)</td>
<td>More than median</td>
<td>25</td>
<td>46.2 ± 13</td>
<td>4.3 ± 1</td>
</tr>
<tr>
<td></td>
<td>Less than or equal to median</td>
<td>25</td>
<td>54.9 ± 15</td>
<td>4.4 ± 1</td>
</tr>
<tr>
<td>All patients (median 14 months)</td>
<td>More than median</td>
<td>45</td>
<td>45.6 ± 14</td>
<td>4.3 ± 1</td>
</tr>
<tr>
<td></td>
<td>Less than or equal to median</td>
<td>53</td>
<td>52.1 ± 15</td>
<td>4.3 ± 1</td>
</tr>
</tbody>
</table>

*Data inadequate for one subject in each group.

References


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