A randomized controlled trial of treatment options for troublesome uterine bleeding in Implanon users

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BACKGROUND: Pilot data have indicated that both doxycycline alone and mifepristone combined with ethinyl estradiol (EE) are effective in stopping episodes of bleeding in Implanon users with troublesome bleeding. We compared four treatments against a placebo in Implanon users and tested whether repeated treatment improved subsequent bleeding patterns.

METHOD: Implanon users aged 18–45 years were randomized to treatment with (i) mifepristone 25 mg given twice on day 1 followed by 4 days of EE 20 μg; (ii) doxycycline 100 mg twice daily for 5 days; (iii) mifepristone 25 mg given twice on day 1 plus doxycycline 100 mg twice daily for 5 days; (iv) doxycycline 100 mg twice daily with EE 20 μg daily; and (v) placebo twice daily for 5 days. The primary end-point was the number of days of bleeding/spotting immediately following initiation of the first 5-day course of each therapy, compared with placebo.

RESULTS: There were 204 women assigned to treatment. Mifepristone in combination with either EE or doxycycline was significantly more effective in stopping an episode of bleeding (mean 4.0 days (CI 3.5–4.6) and 4.4 days (CI 3.8–5.2), respectively) than doxycycline alone or in combination with EE, or placebo (6.4 days (CI 4.4–9.2), 6.4 days (CI 4.8–8.6) and 6.4 days (CI 5.1–8.0), respectively).

CONCLUSION: Mifepristone combined with either EE or doxycycline was significantly more effective than placebo in terminating an episode of bleeding in Implanon users. However there was no improvement in subsequent bleeding patterns. Trial registration number: ACTR # 0126000020628.

Key words: bleeding / ethinyl estradiol / doxycycline / Implanon / mifepristone

Introduction

Long-acting progestogen-only contraceptives have been available for over 40 years and are used by more than 20 million women worldwide (d’Arcangues, 2000). These methods provide highly effective long-term contraception 0.3–1.0% failure rates over 12 months (d’Arcangues, 2000), but cause disturbances in normal menstrual bleeding patterns ranging from no bleeding through infrequent bleeds to irregular, frequent and prolonged bleeding. While many women accept effective contraception may involve a trade-off between benefits and disadvantages, many are unable to tolerate unpredictable, irregular or prolonged bleeding.

Implanon (Organon now part of Schering-Plough Corporation, Kenilworth and NJ, USA) is a highly effective single rod contraceptive system which releases a relatively constant dose of the progestogen, etonogestrel, over a period of up to 3 years. Most Implanon users experience a reduction in the frequency and volume of menstrual bleeding but a substantial minority experience unpredictable and frequent and/or prolonged episodes of bleeding (d’Arcangues et al., 1992). A review of data from eleven clinical trials with Implanon by Mansour et al. (2008) found that 11.3% of users discontinued due to bleeding irregularities, mainly prolonged or frequent irregular bleeding. Similar discontinuation rates for abnormal uterine bleeding have been observed with other implantable progestogen only methods (Hickey and d’Arcangues, 2002).

A wide range of treatments have been trialled to manage abnormal bleeding with progestogen-only contraceptives. While some therapies were able to reduce the duration of a bleeding episode, none resulted in long-term improvement in bleeding patterns once treatment was discontinued (Abdel-Aleem et al., 2007). However, mifepristone (100 mg) given intermittently to Norplant users was able to
reduce episodes of prolonged bleeding compared with placebo (Massie et al., 2004).

The development of an effective short-term treatment regimen which would improve both short and medium term bleeding patterns would be of considerable clinical benefit and may improve both acceptability and continuation rates for these otherwise highly popular contraceptive methods. The ideal therapy would be cheap, easily available and stored and would improve long-term bleeding patterns after a single oral dose. In the search for a treatment that meets these criteria, we carried out a pilot study (Weisberg et al., 2006) comparing three short duration treatment regimens against placebo.

We compared mifepristone alone and in combination with ethinyl estradiol (EE), as well as doxycycline alone, to placebo in 150 Implanon users with objectively demonstrated frequent and prolonged bleeding. The primary outcome was the time to stop a bleeding/spotting episode after starting the treatment intervention. Both mifepristone in combination with EE and doxycycline alone were significantly more effective in stopping an episode of bleeding (mean 4.3 days (CI 3.5–5.2) and 4.8 days (CI 3.9–5.8), respectively) than mifepristone alone or placebo (5.9 days (CI 4.8–7.3) and 7.5 days (CI 6.1–9.1), respectively). However there was no effect on subsequent bleeding patterns from this single treatment (Weisberg et al., 2006).

The aim of the present study was to investigate the efficacy of low doses of mifepristone plus EE, doxycycline alone, mifepristone plus doxycycline plus EE compared with placebo in a larger population of women with prolonged and/or frequent bleeding using Implanon. Further, we wished to determine whether intermittent dosing could improve bleeding patterns over a 90 day reference period (Belsey and Pinol, 1997).

## Methods

Women between the ages of 18–45 years, who had used Implanon for at least 3 months and were experiencing prolonged or frequent bleeding were recruited, either through clinics or by advertisement, at four Australian sites: Sydney Centre for Reproductive Health Research, Research division of Family planning, NSW; King Edward Hospital, Perth; the Royal Women’s Hospital, Melbourne; and Department of Obstetrics and Gynaecology, University of Queensland.

Subjects were excluded if they had any contraindications to the active treatments used. These included a history of heart attack or stroke, thromboembolism, severe liver or kidney disease, blood pressure >160 mm systolic or >95 mm diastolic, focal migraine, breast cancer or any genital cancer, or any possible sensitivity to EE, tetracyclines or lactose. Women taking phenytoin, carbamazepine, phenobarbital, retinoids or vitamin A or unwilling to keep a daily menstrual diary or otherwise unwilling to follow the study criteria were also excluded.

Subjects maintained a daily menstrual diary chart for a minimum of 90 days and were then enrolled into the treatment phase provided they had met one of the World Health Organization criteria for prolonged or frequent bleeding (Belsey and Pinol, 1997) (defined as one episode of bleeding and/or spotting lasting more than 10 days or more than four bleeding/spotting episodes in a 90 day reference period).

This was a randomized, double-blind, placebo-controlled trial. Subjects were randomized to one of the following treatments: (i) mifepristone 25 mg twice daily (Hualin Company, Shanghai, China), plus EE 20 μg (Progon C, Schering AG, Berlin, Germany), (ii) doxycycline 100 mg twice daily (Douglas Pharmaceuticals, Sydney, Australia), (iii) doxycycline 100 mg twice daily plus mifepristone 25 mg, (iv) doxycycline 100 mg twice daily plus EE 20 μg or (v) placebo, according to the regimens shown in Table I. Randomization was computer generated in blocks of 20 with separate randomization schemes for each centre.

The four active treatment regimens and the placebo were packaged identically into opaque gelatin capsules with starch filling (DFC Thompson). The blister pack manufacturer (CPSA) assigned the treatments and placebo as 1, 2, 3, 4 and 5 without reference to the investigators and presented the treatments and placebo in identical foil blister packs containing 10 capsules. The day and time of administration were marked on the back of the pack. Both subject and prescriber were blinded to the treatment allocation. Three identical medication packs were placed in a sequentially numbered and sealed opaque envelope which also contained detailed instructions for taking the drugs. Subjects were instructed to start treatment on the second day of the next bleed and to repeat the treatment at 28 day intervals in the 90-day treatment reference period. All drug packs including any unused capsules were returned at the end of the study or at early termination and compliance was recorded. Subjects continued to keep a menstrual diary for a further 90 days following the ‘treatment’ reference period (the ‘post-treatment’ reference period) to determine the impact of treatment on subsequent bleeding patterns (Fig. 1). Participants were asked to comment on the volume, duration and frequency of their bleeds at their first and their final visits.

In case the randomization code needed to be broken, two sealed ‘master’ envelopes were lodged with the chair of the Data and Safety Monitoring Board and the Chief Executive Officer of FPNSW.

Women were questioned at admission into the study and on completion or withdrawal from the study about their perception of bleeding patterns using standard questions.

### Table I Treatment schedules for the different comparison groups

<table>
<thead>
<tr>
<th>Treatment day</th>
<th>1 (Day 2 of bleeding)</th>
<th>2 (Day 2 + 1)</th>
<th>3 (Day 2 + 2)</th>
<th>4 (Day 2 + 3)</th>
<th>5 (Day 2 + 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>Mife 25 mg bd</td>
<td>100 mg bd</td>
<td>100 mg bd</td>
<td>100 mg bd</td>
<td>100 mg bd</td>
</tr>
<tr>
<td>Group 2</td>
<td>Mife 25 mg bd</td>
<td>100 mg bd</td>
<td>100 mg bd</td>
<td>100 mg bd</td>
<td>100 mg bd</td>
</tr>
<tr>
<td>Group 3</td>
<td>Placebo bd</td>
<td>100 mg bd</td>
<td>100 mg bd</td>
<td>100 mg bd</td>
<td>100 mg bd</td>
</tr>
<tr>
<td>Group 4</td>
<td>Doxy 100 mg bd</td>
<td>Mife 25 mg bd</td>
<td>Doxy 100 mg bd</td>
<td>Doxy 100 mg bd</td>
<td>Doxy 100 mg bd</td>
</tr>
<tr>
<td>Group 5</td>
<td>Placebo pm</td>
<td>Mife 25 mg bd</td>
<td>Placebo pm</td>
<td>Placebo pm</td>
<td>Placebo pm</td>
</tr>
</tbody>
</table>

Mife = mifepristone; EE = ethinyl estradiol; Doxy = doxycycline; bd = twice daily.
The primary end-point was the number of days of bleeding and spotting immediately following initiation of the first 5-day course of each active therapy, compared with placebo, to demonstrate the speed at which an episode of bleeding could be stopped by the study medication.

Secondary end-points were:

- The mean number of days of bleeding and spotting immediately following initiation of the first 5-day course of therapy, compared with the other three therapies.
- The duration (number of days) of the first bleeding/spotting-free interval after the initiation of treatment (compared with placebo, and with the other three treatments) for the first treatment segment.
- The mean number of days of bleeding and spotting during the 90-day ‘treatment’ reference period compared with the pretreatment and the post-treatment reference periods, compared with placebo and the other three treatments (also calculated as percentage reduction).
- The mean number of bleeding/spotting episodes during the 90-day ‘treatment’ reference period compared with the pretreatment and post-treatment reference periods, compared with placebo and the other three treatments (also calculated as percentage reduction).

**Statistical Analysis**

**Power calculation**

Based on our pilot data, we planned to enrol 490 women assigned to five groups with 98 subjects per group to provide a power of 80%, alpha (\(P > \text{threshold}\)) at 0.05, and a small to medium effect size on our main outcome.

Randomization by an independent statistician was performed by computer generation of a random number table for each recruitment centre in blocks of 20 with equal numbers in each of the five groups. The design of this double-blind, randomized, placebo-controlled trial met the criteria proposed by the Consort statement (Altman et al., 2001; Moher et al., 2001).

Analysis was carried out on an intention to treat basis for all enrolled subjects. Statistical analysis of this five-group, randomized trial was carried out with SPSS 16.0 using geometric means and ANOVA with planned contrasts with the primary outcome measure. Statistical tests were conducted with regard to the logs of the values of interest. Accordingly, in the case of two-group comparisons for example, a t-test was performed on the arithmetic mean of the logarithm of the variable of interest (e.g., number of days to stop bleeding). For 95% confidence intervals, the standard error of the logarithm of the outcome variable of interest was multiplied by the z-score for the normal distribution (\(=1.96\)) corresponding to 0.025 of the area under each end of the normal distribution. The resulting quantity was subtracted from (for the lower 95% CI), and added (for the upper 95% CI) to, the arithmetic mean of the logarithm, after which each was anti-logged to base 10 to produce the geometric mean and its corresponding 95% confidence intervals (Altman, 1991).

Ethical approval was given by the Human Ethics Committees of all participating centres. Written informed consent was obtained from all participants prior to entering the study.

**Results**

**Subjects**

There were 278 Implanon users recruited between March 2005 and May 2007 (see discussion regarding numbers of women recruited). Of these 74 were withdrawn prior to randomization: 34 were ineligible, 17 had the Implanon removed early, three had protocol violations, 10 no longer wished to participate, nine were lost to follow-up and one experienced an adverse event (Fig. 2). There was no statistical difference in demographic factors (Table II) nor in the perception of bleeding patterns (Table III) between the women who withdrew and those who were randomized or between the women allocated to different treatment groups (Table III).

There were 204 women randomized: 40 women allocated to placebo, 41 to mifepristone plus EE, 41 to doxycycline alone, 41 to mifepristone plus doxycycline and 41 to doxycycline plus EE (Fig. 2). There was no statistical differences between the five treatment groups in the mean number of bleeding/spotting days or in the mean number of bleeding/spotting episodes in the 90 day pretreatment and 90 day post-treatment phases (data not shown). Data on the duration of the bleed-free interval after treatment 1 were available for 179 treated women. There were 137 of the treated women who completed the full 90 day post-treatment diary. There were no significant differences in withdrawal rates between treatment groups.

Compliance with all five treatments was reasonable. Although 98 women failed to take all capsules during the treatment phase, 63 of these missed only one or two capsules out of the 10 in any treatment period distributed across all treatment groups. There were no pregnancies.
Geometric means ± 95% confidence levels were used for comparison of treatments to allow for the skewed distribution of bleeding/spotting days in all groups. Two active treatment regimens were significantly more effective than the placebo in terminating a bleeding episode (Fig. 3). Mifepristone plus EE and mifepristone plus doxycycline terminated a bleeding episode significantly more effectively within a mean of 4.0 (CL 3.5–4.6) and 4.4 (CL 3.8–5.2) days, respectively, compared with 6.4 (CL 4.8–5.8) for doxycycline plus EE, 6.4 (CL 4.4–9.2) for doxycycline alone and 6.4 (CL 5.1–8.0) days for placebo (P = 0.0008 and 0.0108, respectively) (Table IV and Fig. 3).

Mifepristone when combined with either EE or doxycycline was equally effective in stopping a bleeding episode (Table IV). By 8 days after starting the first treatment, those who had stopped bleeding were: all women in the mifepristone and EE group; 97% in the mifepristone plus doxycycline group, 65.6% in the doxycycline group, 60% in the doxycycline group plus EE and 70.3% in the placebo group (Fig. 3).

There were no significant differences between the treatment groups and the placebo nor between the different treatment groups in the number of bleed-free days after the treatment, in the duration of the first post-treatment bleed, or in the number of bleeding/spotting days or episodes in the 90 day treatment or post-treatment phases.

**Figure 2** Consort participation table.
Table II  Demographic characteristics according to drug allocations

<table>
<thead>
<tr>
<th>Allocation code</th>
<th>Doxycycline</th>
<th>Doxycycline + EE</th>
<th>Placebo</th>
<th>Mifepristone + EE</th>
<th>Mifepristone + doxycycline</th>
<th>Non-randomized</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age mean</td>
<td>28.6 ± 6.8</td>
<td>28.8 ± 6.0</td>
<td>28.8 ± 5.8</td>
<td>29.1 ± 7.2</td>
<td>29 ± 6.0</td>
<td>28 ± 6.3</td>
<td>NS</td>
</tr>
<tr>
<td>Age median</td>
<td>27</td>
<td>26</td>
<td>28.5</td>
<td>29</td>
<td>28</td>
<td>27.5</td>
<td>NS</td>
</tr>
<tr>
<td>No pregnancies (mean)</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>No living children (median)</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>113 ± 16.6</td>
<td>110 ± 13.8</td>
<td>110 ± 9.8</td>
<td>111 ± 16.8</td>
<td>111 ± 10.8</td>
<td>110 ± 10.8</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69.5 ± 14.3</td>
<td>69.3 ± 12.4</td>
<td>71.5 ± 21.9</td>
<td>72.8 ± 26.2</td>
<td>72.5 ± 17.5</td>
<td>70.6 ± 19.0</td>
<td>NS</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167 ± 7.7</td>
<td>165 ± 5.8</td>
<td>166 ± 6.3</td>
<td>167 ± 7.0</td>
<td>165 ± 7.7</td>
<td>165 ±</td>
<td>NS</td>
</tr>
<tr>
<td>Recreational drugs no (%)</td>
<td>18</td>
<td>14 (34.1%)</td>
<td>11 (27.5%)</td>
<td>14 (34.1%)</td>
<td>10 (24.4%)</td>
<td>27 (37.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Smokers no (%)</td>
<td>12 (29.3%)</td>
<td>10 (24.4%)</td>
<td>14 (35.0%)</td>
<td>10 (24.4%)</td>
<td>9 (22.0%)</td>
<td>29 (39.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Education level</td>
<td>No school</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Primary</td>
<td>1 (2.4%)</td>
<td>1 (2.4%)</td>
<td>2 (5.0%)</td>
<td>0</td>
<td>1</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td></td>
<td>High school</td>
<td>15 (36.6%)</td>
<td>14 (34.1%)</td>
<td>13 (32.5%)</td>
<td>13 (31.7%)</td>
<td>25 (34.2%)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Technical/vocational</td>
<td>14 (34.1%)</td>
<td>9 (22.0%)</td>
<td>6 (15.0%)</td>
<td>10 (24.4%)</td>
<td>9 (22.0%)</td>
<td>27 (37.0%)</td>
</tr>
<tr>
<td></td>
<td>University</td>
<td>11 (26.8%)</td>
<td>17 (41.5%)</td>
<td>19 (47.5%)</td>
<td>18 (43.9%)</td>
<td>19 (47.5%)</td>
<td>20 (19.4%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>ATISIC</td>
<td>2 (4.9%)</td>
<td>0</td>
<td>1 (2.5%)</td>
<td>1 (2.4%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Caucasian</td>
<td>35 (85.4%)</td>
<td>37 (90.2%)</td>
<td>34 (85.0%)</td>
<td>38 (92.7%)</td>
<td>39 (95.1%)</td>
<td>71 (95.6%)</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>2 (4.9%)</td>
<td>2 (4.9%)</td>
<td>1 (2.5%)</td>
<td>2 (4.8%)</td>
<td>1 (2.4%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>2 (4.9%)</td>
<td>2 (4.9%)</td>
<td>4 (10.0%)</td>
<td>0</td>
<td>1 (2.4%)</td>
<td>2 (2.7%)</td>
</tr>
</tbody>
</table>
The percentage reductions in the mean number of bleeding and spotting days in the 90 day treatment phase compared with pretreatment were 17.7% for placebo, 22% for mifepristone plus EE, 25.7% for mifepristone plus doxycycline and 5.5% for doxycycline alone, while there was an increase of 4.5% for doxycycline plus EE.

Almost three-quarters of the women changed their perception of their bleeding patterns following treatment and this did not differ significantly between the groups (62% in the mifepristone plus EE group, 75% in the mifepristone plus doxycycline group, 70% with doxycycline alone, 82% in the doxycycline plus EE group and 71% in the placebo group) ($P = 0.729$). Before treatment, 85.3% of Implanon users studied felt that the duration of their bleeding was ‘too long’. Following treatment 57.5% still felt that the duration of their bleeding was ‘too long’. Before treatment, 82.8% of Implanon users felt that the interval between bleeding episodes was ‘too short’. Following treatment 49.5% still felt that the interval between bleeding episodes was ‘too short’.

There were no serious adverse events related to study drug administration but one woman withdrew from the study to undergo a partial thyroidectomy. Women in each treatment group reported a wide range of minor side effects, the most common of which were nausea and headaches.

Nausea occurred in eight women using doxycycline, in three using doxycycline plus EE, in six on placebo and in five on doxycycline plus mifepristone. Only one of these women (in the placebo group) stopped medication due to nausea. Headaches were most common in the women taking doxycycline plus EE: nine women were affected compared with two in the placebo group, four in the doxycycline plus mifepristone group and three in the doxycycline group. Other side effects which occurred less commonly included vomiting, diarrhoea, heartburn, abdominal cramps or bloating, vaginal discharge or itch, acne, extreme tiredness and hot flushes. Gastro-intestinal upsets, although infrequent, were more common in the groups taking doxycycline.

### Discussion

The main finding from this study is that a relatively low dose (25 mg) of mifepristone in combination with EE (20 µg) is effective in shortening a bleeding episode in Implanon users with prolonged and/or frequent bleeding. All the women in this group stopped bleeding within 8 days of starting treatment and over 50% stopped within 4 days. Mifepristone alone at higher doses has previously been shown to be effective in reducing the duration of bleeding with other progestogen-only implants (Cheng et al., 2000; Massie et al., 2004). This study confirms our pilot data that a lower dose of mifepristone plus EE is effective in stopping an episode of bleeding. Our decision to add EE to mifepristone was an attempt to maximize the efficacy of estradiol in stimulating endometrial epithelial proliferation by first up-regulating estrogen receptors using mifepristone (Glassier et al., 2002) before given EE. Also, our pilot data did not demonstrate any superiority of mifepristone 25 mg alone over placebo (Weisberg et al., 2006). It is possible that a higher dose of mifepristone alone may have been more effective.

Experimental data from a mouse model of endometrial breakdown and repair (Morison et al., 2007) have demonstrated that mifepristone
is highly effective at enhancing rapid repair of the endometrium in the presence of an Implanon-like device (Morison et al., 2008). This may explain the rapid and effective response to mifepristone in our two dosage groups. Mifepristone combined with doxycycline was almost as effective as the EE combination. In this group, 97% stopped bleeding within 8 days of starting treatment and the remaining woman stopped on the ninth day. For 40% bleeding stopped within 4 days.

Altered endometrial matrix metalloproteinase (MMP) activity appears to predispose to irregular vessel breakdown and bleeding and vascular fragility in progestogen users, and non-vascular elements of the endometrium regress with continuous progestogen exposure. Continuous low-dose progestogens create an endometrium with increased and disordered micro-vessels, decreased stromal and glandular support and reduced epithelial integrity (Livingstone and Fraser, 2002). The structural compromise of these micro-vessels in an environment of increased protease activity results in vascular fragility, instability of the surface epithelium and hence abnormal uterine bleeding (Hickey et al., 2000).

Tetracyclines can inhibit MMPs in a dose-dependent manner by mechanisms independent of their anti-microbial activity (Vernillo et al., 1994) and it is now apparent that there is a broad spectrum of mechanisms by which tetracyclines might inhibit MMP-mediated matrix degradation. Doxycycline is a potent MMP inhibitor which reduces the likelihood of MMP release and tissue breakdown and is cheap, stable at room temperature and widely available. We were disappointed that this larger trial did not confirm the findings from our pilot study that doxycycline alone was effective in terminating a bleeding episode (Weisberg et al., 2006). Parallel studies in a mouse model of endometrial breakdown and repair (Morison et al., 2007) have also failed to demonstrate that doxycycline is effective in endometrial repair in the presence of etonogestrel (Salamonsen et al., unpublished data). This suggests that while activity of MMP may contribute to the process of endometrial breakdown and bleeding, purely blocking some MMPs may not be sufficient to prevent or reverse this process.

This larger study failed to repeat two findings from our pilot data: that doxycycline alone or combined with EE would effectively stop a bleeding episode. We examined a number of possible confounders due to chance effects of the randomization procedure, but found that there were no differences between the groups in the duration of Implanon use prior to treatment, or in the number of women who had more than 60 days of bleeding in the pretreatment phase. We also checked unused capsules in both trials to confirm that randomization was correct. The dosage and manufacturer of the doxycycline were identical to the pilot trial and only the batch number differed.

We hypothesized that combining the progestogen receptor antagonising effect of mifepristone with the MMP inhibiting capability of doxycycline would reduce matrix degradation in the endometrium, maximize regeneration and hence improve bleeding patterns in Implanon users. However, the efficacy of stopping a bleeding episode in the mifepristone plus doxycycline group was identical to that in the mifepristone plus EE group. We were unable to compare the efficacy of mifepristone plus doxycycline with mifepristone alone in this trial. In

![Figure 3](image-url)

**Figure 3** Total number of days to stop bleeding according to drug allocation from the day of starting the first treatment (median plus 25th and 75th percentiles).
comparing the results for time bleeding to stop between our pilot study and the main study, there were virtually no differences between the two mifepristone + EE groups (Fig. 4). The doxycycline alone group behaved similarly up to 8 days after initiation of treatment with no outliers in the pilot, but with seven outliers in the main study. The placebo group also behaved differently in the two studies with nine prolonged outliers in the pilot and five in the main study (Fig. 4).

The number of subjects completing this main trial may have been a factor in the failure of this study to confirm our pilot study findings regarding the effectiveness of doxycycline, although the power for the main outcome factor (time to stop bleeding from the start of the first treatment) was 92% for mifepristone plus EE, and 72% for mifepristone plus doxycycline. The original aim was to recruit 500 women, with 100 in each group to give adequate numbers to confirm or disprove our previous findings. Unfortunately recruitment for this study proved much more difficult than for our pilot study. We recruited all subjects for the pilot study over a period of 12 months, whereas in this study we had to stop recruiting after 26 months due to funding restrictions without achieving our planned sample size. At the time of our pilot study Implanon had only recently been marketed in Australia and little information about bleeding patterns was available to the general public. Following delays in obtaining an import license and a new supply source of mifepristone, by the time we were ready to start the main study, many women were aware of the fact that if troublesome bleeding had not improved within 3–6 months of Implanon insertion it was unlikely to do so, and opted for early removal. As a result, recruitment was difficult and slow with a considerable number of women withdrawing during each phase of the study mainly to have the Implanon removed prematurely (Fig. 2). The withdrawal rate during the treatment and follow-up phases of the study probably reflect the absence of long term improvement in bleeding patterns.

Almost three-quarters of the women changed their perception of their bleeding patterns following treatment, but this did not differ significantly between the groups. The improvement in perception of bleeding by subjects was noted in all treatment groups, including the placebo, a finding previously noted by d’Arcangues (2000) and in our own pilot study. These reports indicate that perception does not relate closely to the actual number of days of bleeding or spotting in Implanon users.

A potential consequence of using multiple doses of mifepristone and EE in conjunction with Implanon is the possibility of loss of contraceptive efficacy by the combined action of a progesterone receptor modulator increasing the possibility of ovulation and estrogen counteracting the cervical mucus protection. We are encouraged that no pregnancies have been reported in small studies using repeated higher doses of mifepristone (50 mg) and only one pregnancy was reported in a woman using Norplant in a study using mifepristone 100 mg for 2 days at monthly intervals over a period of 6 months (Cheng et al., 2000; Massie et al., 2004). We are currently evaluating whether mifepristone 50 mg alone and in combination with EE 20 μg interferes with the contraceptive function of Implanon. An interim analysis in this study suggests that the contraceptive efficacy of Implanon is unaffected by this treatment (Weisberg et al., unpublished data).

In summary, this double blind randomized, placebo-controlled trial has demonstrated that both mifepristone plus EE and mifepristone...
plus doxycycline are effective in terminating a bleeding episode in Implanon users with frequent and/or prolonged bleeding. However, we have not shown any effect of intermittent medication with these, or any other novel treatment regimens, in improving subsequent bleeding patterns.

Clearly, much more basic research needs to be undertaken to try and understand the underlying mechanisms within the endometrium which lead to some women developing fragile superficial blood vessels and compromised superficial epithelium, while the majority do not have this problem.

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Conflicts of interest: E.W. has occasionally served on an Organon Advisory panel. D.P. has received occasional lecture fees from Organon. I.F. has received occasional lecture, clinical
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**References**


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