Management of irregular uterine bleeding and spotting associated with Norplant®

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Norplant®, a systemic contraceptive, has been used extensively throughout the world. A major problem for consumers utilizing Norplant has been irregular, unpredictable uterine bleeding or spotting. This study seeks to determine whether or not an appropriate treatment could be found that will reduce the incidence of spotting and bleeding.

Both a pilot study and an interim report of a multi-center trial utilizing ethinyl estradiol 20 μg for 10 days, versus Ibuprofen 800 mg three times a day for 5 days, versus placebo is reported. Based on the interim analysis of the multi-center trial, there is a reduction in the mean number of spotting days with one of the three treatments compared to the other two treatments (p = 0.044). There was no difference in the number of bleeding days between treatment regimens.

It appears from a review of the literature that both oestrogen, progesterone, and non-steroidal anti-inflammatory agents may reduce the number of bleeding days or inhibit acutely the bleeding in women utilizing Norplant. The completion of this randomized multi-center trial will hopefully give us further insight into an effective treatment for controlling the irregular bleeding and/or spotting that occurs in Norplant users.

Keywords: ethinyl oestradiol/ibuprofen/Norplant/uterine bleeding

Introduction

Norplant® has been used extensively as a contraceptive agent throughout the world. All the reports on its introduction and use in a variety of countries and settings have indicated that somewhere between 20 and 30% of users experience irregular, unpredictable uterine bleeding (Table I) (Du et al., 1990; Akhter et al., 1993; Gerber et al., 1994; GuJuan et al., 1994; Pasquale et al., 1994; Sivin, 1994; Noerpramana, 1995). Approximately one-third of users experience no bleeding whatsoever, and this in itself raises some concerns for the woman as to whether she is pregnant. Counselling and reassurance that lack of menses is a known side-effect results in improved acceptance by women. Irregular bleeding is the principal side-effect associated with the utilization of Norplant. There is an increased incidence of menstrual cycle disruption with the use of any progestin-only contraceptive, including DepoProvera® (Upjohn Co., Kalamazoo, MI, USA). Even combination oral contraceptives containing both an oestrogen and a progestin ultimately result in irregular uterine bleeding when administered continuously. The pathophysiology of irregular uterine bleeding is currently not known, and its management, to date, has been empirical. In fact, the lack of an effective technique for the control of irregular bleeding contributes significantly to the premature removal of Norplant.

The extent of uterine bleeding, even though it can be persistent and prolonged, is usually not clinically significant. No studies have documented anaemia or even a significant drop in haemoglobin concentrations in Norplant users. In fact, the converse is found: haemoglobin concentrations rise in Norplant users (Sivin, 1994). Uterine bleeding or spotting, which occurs erratically, frequently and for >5–6 days, is more of a nuisance rather
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Table I. Incidence of bleeding in the first year of Norplant use, and percentage discontinuation for other medical reasons

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of volunteers</th>
<th>Percentage with bleeding in first year (%)</th>
<th>Percentage discontinuation for other medical reasons (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sivin (1994)</td>
<td>Not given</td>
<td>40-50</td>
<td>&lt;15</td>
</tr>
<tr>
<td>Du et al. (1990)</td>
<td>1361</td>
<td>60.5</td>
<td>2.2</td>
</tr>
<tr>
<td>Gerber et al. (1994)</td>
<td>208</td>
<td>Not given</td>
<td>2.8</td>
</tr>
<tr>
<td>Akhter et al. (1993)</td>
<td>600</td>
<td>15</td>
<td>NA</td>
</tr>
<tr>
<td>Pasquale et al. (1994)</td>
<td>75</td>
<td>35</td>
<td>Not given</td>
</tr>
<tr>
<td>Gu-Juap et al. (1994)</td>
<td>10,718</td>
<td>Not given(^a)</td>
<td>2.37</td>
</tr>
<tr>
<td>Noerpramana (1995)</td>
<td>170</td>
<td>12.3</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)See references for details.
\(^b\)5.4% annual termination for bleeding.

than a problem of any medical significance, interfering with the personal life and hygiene of the consumer. To dramatize this point, this author knows of no studies that would indicate that a dilatation and curettage and/or any other operative procedure should be performed on those women who have persistent irregular bleeding/spotting when using a progestin-only contraceptive.

There is no need to carry out diagnostic studies, such as an endometrial biopsy or even a transvaginal ultrasound for endometrial thickness, in a Norplant user experiencing usual bleeding and spotting. The reason for this is that previous studies have shown no evidence of any significant abnormal endometrial change on histological evaluation. The endometrium in Norplant users is usually characterized by histology in terms of 'suppressed', 'inhibited' or 'progestationally dominant' (Johannisson, 1990). These terms reflect the histological findings of a thin endometrial lining, with sparse tubular glands, without mitotic activity or secretion, with the surrounding stroma showing evidence of decidualization and/or oedema. Attempts to relate the endometrial histology and/or morphometric analysis of the endometrium to the occurrence of bleeding/spotting have proved unsuccessful (Johannisson, 1990). Despite the fact that irregular bleeding is so prevalent when using progestin-only contraceptives, no medical management has gained acceptance for its treatment.

There are two published studies investigating medical treatments in a prospective randomized trial carried out in women using Norplant (Diaz et al., 1990; Alvarez-Sanchez et al., 1996). One study found that women who were administered ethinyl oestradiol (50 \(\mu\)g/day) for 20 days had a 40% reduction in the number of bleeding and spotting days compared with women receiving placebo over a 1 year time period (Diaz et al., 1990). It should be noted that this treatment did not cure the irregular bleeding. The average number of oestrogen treatments over the 1 year period was 2.2 per woman. There was no statistically significant difference between the oestrogen and placebo users in terms of the number of medication refills. The utilization of oestrogen in this study stopped uterine bleeding in a majority of women within 5 days of initiating treatment (Diaz et al., 1990).

This report also had two other therapeutic arms: 800 mg ibuprofen (NSAID) administered three times a day for 5 days; and 300 \(\mu\)g levonorgestrel administered twice a day for 20 days. Both of these treatments resulted in a 30% reduction in the number of bleeding and spotting days compared with women given placebo (Diaz et al., 1990). It is apparent that there are several different therapies that could result in a reduction in the duration of uterine bleeding. Despite the different treatment options, there is still a need for future treatment because irregular uterine bleeding or spotting can persist in some women. It should be noted that the major drawback to the use of oral ethinyl oestradiol in this study was in the 20 days that the medication was administered. This resulted in a treatment similar to using a combination oral contraceptive in terms of the concomitant administration of both oestrogen and progestin for contraception.

The second prospective study compared ethinyl
oestradiol alone with ethinyl oestradiol plus levonorgestrel (a combination oral contraceptive) and a placebo. The ethinyl oestradiol was a 50 μg daily dose. Bleeding and spotting were stopped sooner (within 5 days) with the combination oral contraceptive than with ethinyl oestradiol alone. Only acute treatment of the bleeding was reported (Alvarez-Sanchez et al., 1996).

Here we report the result of a pilot study, as well as an interim analysis of a much larger multicentric trial, designed to investigate two medical treatments for the irregular bleeding/spotting associated with Norplant use. The treatment in the pilot study was 20 μg ethinyl oestradiol for 10 days. The treatment arms chosen for the multicentric trial were an oestrogen, ethinyl oestradiol, 20 μg for 10 days, and a non-steroidal anti-inflammatory agent, NSAID, 800 mg daily for 5 days.

The pilot study
Because of the extent of irregular bleeding/spotting in Norplant users and the reported efficacy of ethinyl oestradiol, a pilot study was initiated to investigate the effects of 20 μg ethinyl oestradiol administered daily for 10 days to stop or reduce the bleeding and/or spotting in Norplant users. This dose and duration of ethinyl oestradiol was chosen to reduce the exposure to exogenous oestrogen so as to circumvent the impression of recreating a combination steroidal contraceptive and to decrease the total dose of ethinyl oestradiol. The pilot study was an open-label, single drug, non-randomized clinical trial.

Materials and methods
The following inclusion criteria were used for this study: (i) Norplant inserted between 4 and 24 weeks prior to clinical assessment and enrolment; (ii) bleeding and/or spotting >7 consecutive days or >10 days in a 2 week period; (iii) volunteer’s willingness to participate in the trial; (iv) volunteer’s ability to keep an accurate menstrual diary for the study; and (v) a negative urine pregnancy test.

Our exclusion criteria were: (i) contraindication to any oestrogen therapy; (ii) inability or unwillingness to keep a menstrual diary; and (iii) previous treatment for Norplant-related bleeding.

In all, 20 women were enrolled in the pilot study. The duration of follow-up averaged 8 months.

Results
Of the 20 women who were enrolled in the trial, four never took the medication and appeared to stop bleeding on their own. Of the 10 women who took the ethinyl oestradiol, five stopped bleeding within 5 days of the initiation of oral medication. Another two women had persistent irregular bleeding throughout the oestrogen treatment; one had a uterine fibroid, and the other was on anticoagulant therapy because of a previous replacement of the aorta for Marfan’s syndrome. Four other women were lost to follow-up.

The average interval before cessation of bleeding or spotting was 3.1 days. The average number of treatments over the 8 month period was 2.6 per volunteer. All of the volunteers experienced uterine re-bleeding when they stopped the ethinyl oestradiol treatment after 10 days. We have called this bleeding/spotting after treatment ‘re-bleeding’ to distinguish it from spontaneous bleeding or spotting. The average duration of these re-bleeding episodes was 5.5 days.

Our preliminary experience indicated that oral ethinyl oestradiol appeared to be an effective means of reducing uterine bleeding or spotting. Secondly, it was obvious that a second episode of uterine bleeding occurred when the ethinyl oestradiol was discontinued. The volunteers were instructed about this re-bleeding so that they would not re-initiate treatment just on the basis of this episode. We asked the volunteers not to re-initiate a second treatment until they met the same inclusion criteria of the total number of days of bleeding/spotting in a 2 week period that had been used for their enrolment. In this small group of women, the ethinyl oestradiol was well tolerated and no significant side-effects were identified.

Discussion
Treatment of irregular bleeding and spotting within the first 1–2 years after insertion of the Norplant implant is necessary to enhance compliance. Only two studies have been reported, both of which
used 50 μg/day ethinyl oestradiol orally for 20 days (Diaz et al., 1990; Alvarez-Sanchez et al., 1996). Using this approach, uterine bleeding was rapidly brought under control. Our limited data using 20 μg/day ethinyl oestradiol for 10 days resulted in a comparable cessation of bleeding within 5 days (average 3.1 days) in eight of 10 women (Archer, 1995). These data would support using the lower dose of ethinyl oestradiol in Norplant users.

The utilization of a combination oral contraceptive containing 50 μg ethinyl oestradiol and 250 μg levonorgestrel per day was found to result in a significantly shorter period of bleeding (2.6 days) following the initiation of treatment (Alvarez-Sanchez et al., 1996). The drawback to this approach is that it requires the women to use two separate hormonal contraceptive therapies. The authors of this paper rightfully point out that this treatment is limited to a small proportion of patients for a short time. There was no information in their paper on the percentage of women who required re-treatment for a second episode of uterine bleeding.

This is in contrast to a Norplant user using ethinyl oestradiol, where an average of 2.2 treatments in 1 year for the volunteers was reported (Diaz et al., 1990). This need for re-treatment in a subgroup of women was substantiated when the group receiving placebo were treated an average of 3.1 times and the NSAID group an average of 3.5 times in the 1 year follow-up.

From these data, it appears that there is a need for a reliable, effective therapy for managing the initial irregular bleeding associated with Norplant contraception. Because of this, a multicentric trial was designed and initiated (see below).

**Multicentric, prospective, randomized clinical trial**

The results of our pilot study were positive, so it was decided to initiate a multicentric trial utilizing 20 μg/day ethinyl oestradiol for 10 days. We enrolled women in a placebo arm and a third arm using 800 mg NSAID five times a day. Thus, we designed a triple-blinded, prospective, randomized, multicentric trial to determine whether the identified treatments had any impact on the incidence or duration of bleeding and/or spotting in Norplant users. It was anticipated that if we could identify an effective treatment to control irregular bleeding, this could result in enhanced consumer compliance with Norplant.

**Materials and methods**

**Clinical sites**

Five clinical sites within the USA were identified, with the principal investigators shown in parentheses: The Jones Institute for Reproductive Medicine, Norfolk, VA, USA (David F. Archer); Bowman Gray School of Medicine, Winston-Salem, NC, USA (Thomas Stovall); The Greater Baltimore Medical Center, Baltimore, MD, USA (Vanessa Cullins); University of South Carolina School of Medicine, Columbia, SC, USA (Janice Barpn); and Medical University of South Carolina, Charleston, SC, USA (Adam Levine).

**Experimental design and methods**

To be considered for the study, the women must have met all of the inclusion criteria and exhibited none of the exclusion criteria.

The following inclusion criteria were used: (i) Norplant inserted >4 weeks prior to enrolment in the study; (ii) extensive bleeding and/or spotting (>7 consecutive days or >10 days in a 2 week period); (iii) willingness to participate in a placebo-controlled study; (iv) willingness to keep an accurate menstrual diary card; and (v) Norplant use of <3 years.

The following exclusion criteria were used: (i) contraindications to oestrogen therapy; (ii) inability or unwillingness to keep a menstrual diary card; (iii) unwillingness to participate in a placebo-controlled study; (iv) contraindications to non-steroidal anti-inflammatory agents; (v) previous treatment for Norplant-related bleeding; (vi) chronic use of NSAID (more than two tablets three times a week); and (vii) use of Depo-Provera within 4 months prior to Norplant insertion.

**Medication**

Ethinyl oestradiol (20 μg) tablets with an identical-appearing placebo were supplied by Schering-Plough Pharmaceuticals (Liberty Corner, NJ, USA). NSAID 800 mg tablets and identical placebo tablets were supplied by Upjohn Pharmaceutical Company.

The treatments were in 10-day segments, and
Table II. Diagrammatic representation of the three treatment arms

<table>
<thead>
<tr>
<th>Days</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment I</td>
<td>Ethinyl oestradiol (20 μg oral daily)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Treatment II</td>
<td>Placebo</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen (800 mg oral three times per day)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Treatment III</td>
<td>Placebo</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

There were three separate treatment arms. Treatment arm A involved 20 μg/day ethinyl oestradiol for 10 days, with 5 days of placebo NSAID tablets three times a day. Treatment arm B consisted of 10 days of placebo ethinyl oestradiol tablets and 5 days of 800 mg NSAID three times a day. Treatment arm C consisted of 10 days of placebo ethinyl oestradiol once daily and 5 days of placebo NSAID tablets three times a day.

A diagrammatic representation of the three treatment arms is shown in Table II.

Each volunteer in the study was given enough medication for two treatment cycles with the following instructions. (i) If the bleeding persisted throughout the 10 day treatment, she should take a second 10 day course of treatment immediately. (ii) If the bleeding stopped, she was to wait until she had had a second episode of bleeding that lasted either 7 consecutive days in duration or ≥10 days of bleeding in a 2 week period, at which time she could re-initiate the study medication.

Interim visits were planned every 3 months, with retrieval of the menstrual diary cards at each visit.

Menstrual diary cards and definition of bleeding and spotting

Standard menstrual diary cards were developed to record the number of days of treatment and the number of days of bleeding or spotting in any calendar month. These cards were collected every 3 months from the volunteers. The World Health Organization criteria for bleeding and spotting were used during this study. Bleeding was defined as the need for sanitary protection (pads or tampons), while spotting was based on light staining of underwear not requiring sanitary protection.

Statistical analysis

All bleeding and spotting days and the medication history were entered into a database. An interim analysis was carried out between December 1995 and March 1996, and the treatment codes were not broken. Analyses of variance and covariance were performed to see if there were any differences within the study population.

Results

There were 44 volunteers who had data entered as of December 21, 1995. Their interim results are shown below. There were three groups (A, B and C) that the statistician identified by treatments without breaking the code. These groups did not correspond to the three treatment groups (I, II and III) described in Materials and methods above. The reason for this is that the randomization has not been broken and the investigators do not know the relationship of treatment groups I, II and III to the statistical results identified as A, B and C.

Bleeding days

The mean number of bleeding days for all volunteers was 1.55 after treatment was initiated. Three different groups were identified based on their treatment assignments (Table III). The treatment code was not broken for this interim analysis. The actual treatments are not known, and groups A, B and C are in no way related to the treatments described as I, II and III in Materials and methods. There was no statistically significant
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### Table III. Mean number of days of bleeding and spotting after the initiation of treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean no. of bleeding days</th>
<th>Mean no. of spotting days</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1.85</td>
<td>0.50*</td>
</tr>
<tr>
<td>B</td>
<td>1.36</td>
<td>1.18</td>
</tr>
<tr>
<td>C</td>
<td>1.47</td>
<td>1.44*</td>
</tr>
</tbody>
</table>

Groups were arbitrarily assigned letters A, B and C, which do not correspond to the treatment groups (I, II and III). The treatment code was not broken for this interim analysis.

*Statistically significant difference \( P = 0.044 \).

### Table IV. Number of bleeding days in each group during the first half of treatment (days 1–5) versus the second half of treatment (days 6–10)

<table>
<thead>
<tr>
<th>Group</th>
<th>Days 1–5</th>
<th>Days 6–10</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2.31 ± 2.39</td>
<td>1.38 ± 1.98</td>
</tr>
<tr>
<td>B</td>
<td>1.50 ± 1.99</td>
<td>1.21 ± 1.72</td>
</tr>
<tr>
<td>C</td>
<td>1.76 ± 1.56</td>
<td>1.17 ± 1.42</td>
</tr>
</tbody>
</table>

The groups have been arbitrarily assigned letters A, B and C, which do not correspond to the treatment groups (see text for details).

### Table V. Number of spotting days (mean ± SD) in each arbitrary group comparing days 1–5 with days 6–10 following the initiation of treatment (see text for details)

<table>
<thead>
<tr>
<th>Group</th>
<th>Days 1–5</th>
<th>Days 6–10</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.23 ± 0.44*</td>
<td>0.77 ± 1.59</td>
</tr>
<tr>
<td>B</td>
<td>1.64 ± 1.95</td>
<td>0.71 ± 1.44</td>
</tr>
<tr>
<td>C</td>
<td>1.94 ± 1.34*</td>
<td>0.94 ± 1.43</td>
</tr>
</tbody>
</table>

*Statistically significant difference \( P < 0.052 \).

The mean number of bleeding days in each treatment group was analysed further by evaluating the first 5 days (days 1–5) against the second 5 days (days 6–10) of treatment. The mean number of bleeding days was 1.34 in the first 5 days versus 0.82 during the second 5 days of treatment (\( n = 44 \)). The number of bleeding days (mean ± SD) for each group for the first versus the second 5 days of treatment are shown in Table IV. There was no significant difference between groups or between treatment intervals.

**Spotting days**

The mean number of spotting days was 1.08 in the volunteers during the treatment period. Group A experienced a mean of 0.50 days of spotting compared with groups B (1.18) and C (1.44) (Table III). There was a statistically significant difference in the mean number of spotting days between groups A and C (\( P = 0.044 \)). There was no difference between groups A and B or between groups B and C (Table III).

The mean number of spotting days was reduced in group A (0.23 ± 0.44) compared with group C (1.94 ± 1.34) (\( P < 0.052 \)) during the first 5 days of treatment (Table V). There was no difference in the mean number of spotting days during days 6–10 after treatment between the three groups (range 0.77–0.94) (Table V).

**Discussion**

These data indicate that there is no cure, i.e. total cessation of irregular bleeding/spotting, following the use of any of the medications under investigation. Our data indicate a reduction in the number of spotting days following treatment A compared with treatment C. Conclusions as to which of the exact medications resulted in this finding cannot be drawn at this time.

The exact mechanism(s) that results in bleeding and/or spotting which occurred when using progestin-only contraceptives is not well characterized. Papers by other authors in this Supplement indicate the breadth of research being carried out to determine the exact cause(s) of bleeding in progestin-only contraceptive users.

It should be re-emphasized that the major cause of discontinuation of a progestin-only contraceptive (Norplant) is menstrual irregularity. It appears that, although not able to alter the contributing underlying process, the physician may be able to offer some treatment that may be acceptable to the consumer to reduce bleeding/spotting and enhance compliance with the Norplant method. With this in mind, it appears that the use of oral ethinyl oestradiol or ethinyl oestradiol plus levonorgestrel can stop the bleeding/spotting that occurs in Norplant users. The reduction in bleeding/spotting reported with these treatments relates to cessation of the acute episodes of bleeding/spotting. These treatments do not alter the underlying pathophysio-
logical process contributing to uterine bleeding/spotting episodes. It is possible that the use of a non-steroidal anti-inflammatory agent (ibuprofen) or levonorgestrel alone can also result in a reduction in the total number of bleeding and/or spotting days during Norplant use.

Our interim data do not allow us to conclude which of the treatments (ethinyl oestradiol, ibuprofen or placebo) in our multicentric trial resulted in the reduction of spotting in our volunteers. Other reports have evaluated the total number of bleeding and spotting days in each treatment arm. When we make a distinction between bleeding and spotting, only spotting was found to be reduced with one of the treatments. We did not find any difference between the group when the total numbers of bleeding and spotting days were evaluated.

Physicians should counsel patients on the use of exogenous oestrogen, ibuprofen or norgestrel, which could result in improvement in their bleeding patterns. Counselling should emphasize the recurrence of irregular bleeding or re-bleeding after treatment.

A definitive answer awaits completion of this trial.

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The authors would like to acknowledge the expert assistance of Mesdames Alice Conti, Barbara Ross, RN, BSN and Eling Gaines in the development and implementation of the protocol. Without the help of the physicians and staff of the clinical trial centres this protocol would not have been possible.

References