Correlation of endocrine profiles with bleeding patterns during use of Nestorone® contraceptive implants

Anibal Faúndes1,4, Francisco Alvarez2, Vivian Brache3, Leila Cochoûn2, Ana Sofia Tejada2 and Alfred Moo-Young3

1Centro de Pesquisas de Doenças Materno-Infantis de Campinas (CEMICAMP), Campinas, SP, Brasil, 2PROFAMILIA, Santo Domingo, Dominican Republic and 3Centre for Biomedical Research, The Population Council, New York, USA

© European Society of Human Reproduction and Embryology

Key words: bleeding patterns/contraceptive implants/ Nestorone®/oestradiol/progesterone

Introduction

New progestins with different metabolic profiles and other attributes are being employed in the development of new subdermal implant systems for contraception in women (Alvarez-Sanchez et al., 1993; Ladipo and Coutinho, 1994). Among them is Nestorone® (NES) (previously known as ST 1435), a potent 19 nor-progesterone derivative, that is not biologically active when administered orally. For this reason, NES is considered an excellent candidate for post-partum contraception in lactating women since the nursing infant is not expected to be at risk, because of the small amount of the steroid in the mother’s milk (Lahteenmaki et al., 1990).

Nestorone® progestin, like other progestin-only contraceptives, causes altered bleeding patterns in women. The most noticeable effect is the increase in the mean number of days of bleeding and spotting in 30 day intervals, with about 25% of users having more than 10 days of bleeding and spotting in each month (Díaz et al., 1995).

Administration of exogenous oestrogen or in combination with a progestin is known to reduce bleeding in women using Norplant® implants (Díaz et al., 1990; Alvarez-Sanchez et al., 1996; Archer et al., 1996). The association between concentrations of endogenous oestrogen and bleeding during the use of Norplant® implants has also been established, and serves as the basis for treatment with ethinyl-oestradiol (Faúndes et al., 1991, 1998). The present study was undertaken to ascertain whether this association between concentrations of endogenous sex steroids and bleeding patterns exists in women who are NES implant users.

Materials and methods

This NES implant study was undertaken at the Department of Biomedical Research of PROFAMILIA, in Santo Domingo, Dominican Republic. The protocol was approved by its Institutional Review Board. All participants read and signed a written informed consent before enrolment in the study.

Two different implant dosages were assessed: a single 4 cm implant containing 80 mg NES (The Population Council, New York, USA) and two 3.0 cm implants, each containing 60 mg NES, delivering approximately 50 and 75 µg/day respectively. The duration of the study was 2 years.

A total of 40 volunteers, 20 in each dose, was recruited among the general population of the clinic. Healthy, sexually active women, with regular menstrual cycles, ages 18–38 years, requiring a contraceptive method, not currently breastfeeding and who voluntarily agreed to participate, were enrolled in this study. Women were requested to maintain a daily bleeding calendar. Ten subjects were dropped from the study for bleeding disturbances or other complaints during the first months of use and another was unable to comply with the blood-sampling schedule. Consequently, only 29 subjects provided the periods of observation for this analysis.

Blood samples were taken twice a week for 6 consecutive weeks at specified time intervals (approximately months 6, 12, 18 and 24). In each sample, oestradiol and progesterone were measured using a solid-phase 125I radioimmunoassay (DPC, Los Angeles, CA, USA). Inter-assay coefficients of variation were 6.52 and 6.06% respectively. Quality control was assured both by the External Quality Assessment...
Scheme for Reproductive Hormones of the World Health Organization and by internal quality control with commercial sera.

The oestradiol and progesterone patterns that preceded bleeding episodes or that corresponded to periods of continuous bleeding or amenorrhoea were analysed retrospectively. Data were collected from 15 and 14 subjects in the low and high dose regimen, respectively. For this study, the data were analysed jointly, because its purpose was to test the possible association between different concentrations of endogenous hormones and bleeding, and not to compare the two systems. As more than one bleeding episode was observed in many subjects, data were obtained in a total of 125 bleeding episodes.

Bleeding periods were categorized as follows: normal length cycles (25–35 days); long cycles (36–90 days); episodes of amenorrhoea longer than 90 days; and short cycles (24 days or less between initiation of two consecutive bleedings). The association between the duration of bleeding (in days) and the preceding hormonal profile was separately analysed as well as the periods of continuous bleeding or spotting for 10 or more days.

Upon evaluation of the available hormonal data related to the bleeding patterns, it was possible to analyse 24 short cycles, 36 normal length cycles, 27 long cycles and nine episodes of amenorrhoea. Blood samples were collected only in the middle of an amenorrhoeic episode in four subjects, only during the last 3 weeks in three women and before and during the last 3 weeks in two. Twenty-eight episodes of prolonged bleeding were separately analysed.

Most of the episodes with amenorrhoea were observed during the first 6 months of use. Short cycles and prolonged bleeding were mostly seen during the first year, while normal length and long cycles were more evenly distributed over the 2 years of observation, although less frequently during the first 6 months of use of the implants.

Student’s t-test was used to evaluate differences in duration of bleeding, and in hormonal concentrations. The correlation coefficient between oestradiol concentrations and duration of bleeding was calculated and a t-test was used to verify its significance.

Results

Hormonal patterns and cycle length

Short cycles were characterized by low oestradiol concentrations, below 350 pmol/l and even less than 175 pmol/l, with the exception of three out of 24 cycles that had samples with oestradiol concentration above 350 pmol/l. No luteal activity was observed in this group (Table I). Progesterone concentrations over 8.0 nmol/l were found in one third of normal cycles and one tenth of long (25–35 days) cycles (Table I). Progesterone concentrations were significantly higher in normal length cycles than in longer cycles (31.2 ± 14.3 versus 10.2 ± 1.9 nmol/l; P = 0.0283).

All six episodes in which samples were taken during amenorrhoea, distant from a bleeding episode, showed oestradiol concentrations consistently below 350 pmol/l. However, two of five of the sampling periods which included the end of the amenorrhoea (last 3 weeks before initiation of bleeding), showed elevation of oestradiol >800 pmol/l before a decline that preceded bleeding. No luteal activity was observed in periods of amenorrhoea.

<table>
<thead>
<tr>
<th>Highest oestradiol (pmol/l) and progesterone (nmol/l)</th>
<th>Cycle length (days)</th>
<th>Short (%) (&lt;25 days)</th>
<th>Normal (%) (25–35 days)</th>
<th>Long (%) (36–90 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oestradiol &lt;175</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progesterone &lt;8.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oestradiol 176–350</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progesterone &lt;8.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oestradiol 351–1500</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progesterone &lt;8.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oestradiol &gt;1500</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progesterone &lt;8.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oestradiol &gt;350</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progesterone &gt;8.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>24</td>
<td>36</td>
<td>27</td>
<td></td>
</tr>
</tbody>
</table>
Table II. Duration of bleeding according to preceding hormonal profile

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Bleeding (days)</th>
<th>Mean</th>
<th>SD</th>
<th>Mean highest oestradiol concentration preceding bleeding (pmol/l)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean</td>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short cycles with</td>
<td>24</td>
<td>4.9</td>
<td>4.1</td>
<td></td>
<td>289.6(^a)</td>
<td>313.5</td>
</tr>
<tr>
<td>no luteal activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(progesterone &lt;8.0 nmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal or long</td>
<td>48</td>
<td>8.8(^b)</td>
<td>3.9</td>
<td></td>
<td>1277.5</td>
<td>823.0</td>
</tr>
<tr>
<td>cycles with no luteal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(progesterone &lt;8.0 nmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal or long</td>
<td>15</td>
<td>5.4</td>
<td>1.4</td>
<td></td>
<td>845.4</td>
<td>352.8</td>
</tr>
<tr>
<td>cycles with luteal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(progesterone &gt;8.0 nmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Significantly different from the other two groups (P = 0.0000).
\(^b\)Significantly different from short cycles with no luteal activity (P = 0.0002); normal or long cycles with luteal activity (P = 0.0016).

**Oestradiol concentrations preceding menses**

The hormonal patterns of women with normal length cycles with or without luteal activity, and with long cycles, were characterized by a rise and fall of oestradiol that preceded bleeding. In contrast, in women with short cycles, bleeding started without discernible change in constantly low oestradiol concentrations (Figure 1). The oestradiol profile was monophasic in long cycles or normal cycles without luteal activity and biphasic in normal length cycles with luteal activity.

**Duration of bleeding**

The duration of bleeding was directly and significantly associated with the highest concentrations of oestradiol observed during the 15 days preceding menses in episodes without luteal activity (r = 0.4007, P = 0.0002) (Figure 2). There were three clear outliers: one with a prolonged bleeding episode (22 days) after a maximal oestradiol concentration of 356.1 pmol/l, and two others with relatively short bleeding episodes (5 and 7 days) after very high oestradiol concentrations above 3500 pmol/l. The correlation was greatly improved (r = 0.6371, P = 0.0000) when these outliers were excluded from the analyses.

Mean duration of bleeding in normal or long length cycles, without luteal activity, was significantly longer (P = 0.0016) than the duration of bleeding episodes that followed normal or long cycles with luteal activity (Table II). This association remained when comparing 14 episodes that could be matched by oestradiol concentrations. The mean number of bleeding days after a bleeding-free interval without a rise in progesterone was 9.0 ± 4.7, versus 5.4 ± 1.4 days after intervals with a rise in serum progesterone over 8.0 nmol/l.

**Episodes of prolonged bleeding**

Prolonged bleeding generally corresponded to periods of relatively low serum oestradiol after high oestradiol concentrations without luteal activity. For the analyses of this process, prolonged bleeding episodes were divided into three periods: the first 3 days, an intermediate period, and the last 3 days of bleeding. Figure 3 shows the mean oestradiol concentrations in each of these three periods, as well as in samples taken the 3 days before and the 3 days after the bleeding episode. The initiation and termination of a prolonged bleeding episode were associated with a pattern of decreasing and increasing concentrations of oestradiol respectively. The oestradiol concentration in the intermediate part of a prolonged bleeding was significantly lower than just before the initiation of the episode (P = 0.0000), than in the initial 3 days of bleeding (P = 0.0047) and than the concentrations just after bleeding stopped (P = 0.03). Three of 21 of these episodes, in which there were samples for evaluation, did not show this pattern at initiation of bleeding. The picture was not as clear at the end of a bleeding episode. Eight of 19 cycles (42%) did not show this pattern, although the mean oestradiol of the samples taken in the first 3 days of the following bleeding free interval was significantly higher than during the mid part of the bleeding episode.

**Discussion**

The results of this study suggest that the ovarian secretion of oestradiol and progesterone during use of NES releasing implants influences the menstrual pattern of the users. Almost
every woman with cycles of normal length, as well as most of those with long cycles, had oestradiol secretion indicative of follicular development and a rise and fall of oestradiol preceded bleeding.

The finding that the higher the oestradiol concentrations in a cycle, the longer the duration of bleeding and that the secretion of progestosterone is associated with shorter duration of bleeding provides additional evidence in support of the hypothesis that, in spite of the continuous administration of NES, endogenous hormones have some influence over the endometrium and the mechanism that controls its bleeding.

The results also indicate that the relationship between endogenous sexual hormones and bleeding is not present in all cases, and that bleeding can start or stop without clear changes in the oestradiol concentrations. Persistently low oestradiol concentrations can coincide with long episodes of amenorrhoea, short cycles and periods of prolonged bleeding. Many times the initiation and the end of short cycles and bleeding episodes after amenorrhoea do not coincide with discernible changes in oestradiol concentrations. This finding of a variety of bleeding patterns with the same low concentration of oestradiol is the apparent reason why several authors have had to disregard the correlation between endogenous sex steroid secretion and bleeding patterns during prolonged use of other progestins (Darney et al., 1996; Fraser et al., 1996).

The rise and fall of oestradiol or oestradiol and progesterone preceding menses in almost every normal length cycle, most long and some short cycles and even at the end of one third of the episodes of amenorrhoea, was consistent. These results disagree with those of Landgren et al. (1981), who did not find significant differences in bleeding pattern or number of bleeding days according to ovarian profile among women using 300 µg of norethindrone orally per day. They used a different form of analysis, however, and pooled women with persistently low and with high oestradiol plasma concentrations (Landgren et al., 1981). On the other hand, the same investigators had found that ‘a major drop in peripheral oestradiol concentrations was associated with withdrawal bleeding within 72 h in five subjects’ using the same method. The observation that bleeding is often observed after a rise and fall of circulating oestradiol has also been described among users of long-acting injectable contraception, either norethindrone enanthate (Goebelsmann et al., 1979) or depo-medroxyprogesterone (Bassol et al., 1984). The latter authors also described low oestradiol concentrations during periods of amenorrhoea or spotting.

In addition, the data presented here confirm that endogenous progesterone secretion is associated with shorter duration of bleeding during use of progestogen-only contraception as has already been observed by other authors (Landgren et al., 1981, 1982).

Comparing this study with one carried out several years ago among Norplant® implant users, the results are very similar (Faúndes et al., 1991). It would be interesting to ascertain if bleeding among users of NES implants can be controlled with oestrogen or combined oestrogen–progestogen administration, as has been described for users of Norplant® implants. In theory, based on the results presented here, it would be possible to obtain similar results.

The mechanism through which sex steroids affect endometrial bleeding is very poorly understood. Apparently, it is not necessarily accompanied by a parallel change in endometrial histology (Kim-Bjorkland, 1991; Landgren et al., 1994) or of endometrial thickness as measured by ultrasound (Olsson et al., 1990; Shaaban et al., 1993; Faúndes et al., 1998). It may be more related to changes in the vascular physiology of the endometrium as suggested by others (Rogers et al., 1993; Googder et al., 1994; Hickey et al., 1998). Nonetheless, independently of the intervention of other factors and of the intimate mechanism of action, the accumulated evidence strongly suggests that female sex steroids continue to play a major role in endometrium bleeding control among women under continuous administration of low doses of contraceptive progestogens.

Acknowledgements

This study was undertaken as part of the contraceptive development programme sponsored and co-ordinated by the International Committee of Contraceptive Research of the Population Council, New York. The financial support provided by the US Agency for International Development, the Rockefeller Foundation, the George Hecht Fund and the Andrew W. Mellon Foundation and the United Nations Fund for Population Activities is gratefully acknowledged.

References


Hickey, M., Dwarte, D. and Fraser, I.S. (1998) Precise measurements of


Received on March 5, 1999; accepted on September 2, 1999