Bleeding pattern and safety of consecutive use of the levonorgestrel-releasing intrauterine system (LNG-IUS)—a multicentre prospective study

K. Gemzell-Danielsson¹, P. Inki², L. Boubli³, M. O’Flynn⁴, M. Kunz⁵, and O. Heikinheimo⁶,⁷

¹Department of Obstetrics and Gynaecology, Karolinska University Hospital, Stockholm, Sweden ²Bayer Schering Pharma AG, Global Medical Affairs Women’s Health, Berlin, Germany ³Hopital Nord, Paris, France ⁴The Practice, Cork, Ireland ⁵Department of Clinical Statistics, Bayer Schering Pharma AG, Berlin, Germany ⁶Department of Obstetrics and Gynaecology, Helsinki University Central Hospital, PO Box 610, 00029-HUS, Helsinki, Finland

⁷Correspondence address. E-mail: oskari.heikinheimo@helsinki.fi

BACKGROUND: The LNG-IUS has increasingly been used for contraception, treatment of menorrhagia and endometrial protection during hormone replacement therapy since mid-1990s. Thus, many women use the LNG-IUS consecutively. However, published data on the bleeding pattern regarding consecutive use of the LNG-IUS is scarce.

METHODS: We performed a prospective 15-month multicentre study on the bleeding profile, removal and insertion procedures and safety of the second LNG-IUS in fertile-aged women who had used their first LNG-IUS between 4 years 3 months and 4 years 9 months and who opted for the insertion of a second IUS immediately after removal of the first IUS. Bleeding data were reported descriptively starting from the last 90 days of the first IUS use and continuing for up to 1 year.

RESULTS: Of the 234 subjects screened, 204 (87%) entered the trial. The median number of bleeding/spotting days during the last 90 days of the first LNG-IUS was 7 (25 and 75% percentiles 0 and 15). Due to bleeding associated with the insertion procedure, this increased to 8 days (4 and 18) during the first 90-day reference period, thereafter decreasing to 4 (0 and 10) days during the second to fourth reference periods. Only one expulsion and no pregnancies, pelvic inflammatory diseases or perforations occurred. A total of 12 subjects (5.9%) prematurely discontinued the study: five due to an adverse event and seven due to other reasons (inclusive of loss to follow-up).

CONCLUSIONS: This study confirms the favourable bleeding profile and safety of consecutive use of the LNG-IUS.

Key words: bleeding profile / insertion / contraception / heavy menstrual bleeding

Introduction

Contraception by means of intrauterine delivery of levonorgestrel (LNG) using the LNG-releasing intrauterine system (LNG-IUS) is highly effective with a Pearl Index of 0.2 at 1 year and a cumulative failure rate of 0.7 at 5 years (Mirena Product Monograph, 2009). Due to its pronounced effects on the endometrium, characterized by suppression of the endometrial glands accompanied by stromal decidualization (Silverberg et al., 1986; Critchley et al., 1998; Phillips et al., 2003), the LNG-IUS is increasingly used also for the treatment of heavy menstrual bleeding (HMB). Randomized prospective studies have indicated that in comparison to hysterectomy or endometrial ablation, treatment of HMB with the LNG-IUS is both acceptable (Hurskainen et al., 2004; Kaunitz et al., 2009) and cost effective (Hurskainen et al., 2004).

The LNG-IUS has been on the market since mid-1990s in most European countries and since 2001 in the USA. The licensed indications of use of the LNG-IUS include contraception, treatment of idiopathic menorrhagia and endometrial protection during estrogen replacement therapy for menopausal symptoms, for which the LNG-IUS has been approved in more than 105 countries (Information from Bayer Schering Pharma AG). The licensed duration of the LNG-IUS use is 5 years. Due to the high continuation rates (Backman et al., 2002; Baldaszi et al., 2003), as well as the reduced menstrual bleeding associated with the use of the LNG-IUS, an increasing number of women opt for a replacement of the LNG-IUS...
after the first 5 years of use. Consequently, more and more women are likely to use more than one LNG-IUS during their reproductive years.

Consecutive use of the LNG-IUS for contraception has previously been evaluated in a single centre study performed at the time of development of the LNG-IUS (Rönnerdag and Odlind, 1999). According to these previous data, a high rate of amenorrhoea (up to 60%) and continuation was seen during the use of the second LNG-IUS. However, some insertion problems, interpreted by the authors to be caused by drying up of the cervical mucus, were observed. In addition, the majority of women in the study were perimenopausal, which could have affected the high amenorrhoea rate observed. The subjects in this trial might also have been exceptionally motivated as they had participated in the LNG-IUS arm of a randomized clinical trial during the first IUS use. To the best of our knowledge, no studies have yet evaluated the consecutive use of the LNG-IUS for the treatment of HMB. Therefore, more data on the safety and efficacy of consecutive use of the LNG-IUS in routine clinical practice are needed.

The objective of the present prospective multicentre study was to characterize the removal and insertion procedure and the bleeding patterns during the first year of use of the second LNG-IUS among fertile-aged women. Moreover, side-effects, continuation rate and reasons for discontinuation were estimated.

Materials and Methods

The present prospective multicentre study was performed at 17 clinics in Finland, France, Ireland and Sweden. There were 25 investigators, all of whom were considered highly experienced at providing the LNG-IUS.

Two hundred women were to be enrolled into the study without formal statistical considerations in order to allow adequate subject number of subjects for efficacy and safety evaluation. The sample size was chosen in order to collect the sufficient bleeding data (in accordance with international guidelines) and data for the secondary outcome measures.

The study was to be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and ICH-GCP Guidelines of 17 January 1997. The protocol and all protocol amendments were to be submitted to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) for review. Protocol amendments implying substantial changes were to be approved by the appropriate IEC/IRB prior to implementation. The planning and conduct of this clinical study were subject to national laws. From the patient population of individual study centres, the investigator was to identify and approach potential candidates for enrolment and subsequent screening. In addition to this, candidates for this study could be recruited by advertising in appropriate local or national newspapers or magazines, where allowed. The study was web-posted at www.clinicaltrials.gov (trial number NCT00393198).

Fertile-aged women who had been using their first LNG-IUS for between 4 years 3 months and 4 years 9 months, either for contraception or for treatment of heavy menstrual bleeding, and who planned to replace the device with a new LNG-IUS were recruited. The inclusion criteria consisted of a signed informed consent, good general health, age between 23 and 45 years and uterine size corresponding to a sound measure of 6–10 cm. A normal cervical smear result within 12 months or at screening, and normal breast palpation findings were required. Mammography was performed for those ≥40 years at screening.

The exclusion criteria included the contraindications to the use of the LNG-IUS (Mirena Product Monograph, 2009). In addition, clinically significant menopausal symptoms or current estrogen therapy, abnormal finding of the endometrium at transvaginal ultrasound examination, ovarian cyst >30 mm in diameter not resolving spontaneously over 8 weeks, history of malignancy, concomitant use of medication which may alter the serum levels of LNG, BMI ≥35 kg/m², substance abuse, participation in another clinical trial within 1 month or intake of an experimental drug within 3 months prior to screening and close affiliation with the investigator or the investigational site were listed in the exclusion criteria.

The study flow is shown in Fig. 1. In brief, the study visits were as follows: following inclusion at the screening (visit 1), filling of the 90-day bleeding diary and an entry visit (visit 2) for removal of the first LNG-IUS and insertion of the second LNG-IUS was scheduled after 90 days. Visit 3 was scheduled at 3 months, visit 4 at 6 months and visit 5 at 12 months following the entry visit. Some of the women (n = 89) participated in a nested, randomized multicentre study assessing the effect of misoprostol versus placebo pretreatment on the removal and insertion procedures. The results of the subset with regards to these procedures are being reported elsewhere (Heikinheimo et al., 2009).

The primary efficacy variable of the study was the bleeding pattern during the last 3 months of use of the first LNG-IUS and during the first year of use of the second LNG-IUS. Bleeding was assessed using a daily bleeding diary, in which bleeding was graded as none, spotting (no need of sanitary protection, or panty liners only), light (need of sanitary protection yet less than menstruation), normal or heavy (more than normal menstruation according to the subjects’ experience). Bleeding was assessed in 90-day episodes. In addition, bleeding/spotting during the 7 days before and after the exchange of the IUS was analysed separately to capture any bleeding/spotting caused by the removal/insertion procedures.

Secondary outcome variables were the assessment of the removal of the first IUS and insertion of the second IUS (by the woman with regards to pain and by the physician with regards to easiness). The pain experienced during the removal and insertion of the LNG-IUS was graded by the women as none, mild, moderate or severe. Ease of the procedures was assessed by the physicians as easy or difficult. These assessments were performed immediately following the removal and insertion.
procedure. Also, potential need for dilatation of the cervix, local anesthe-
sia or pain medication was noted.

The continuation rate during the first year of use of the second LNG-IUS, pregnancy rate, menstrual comfort and user satisfaction (data not presented), occurrence of adverse events (AE) and serious AEs (SAE), were also assessed.

**Statistics**

Women who received the second LNG-IUS, or for whom at least one insertion attempt was made, were included in the full analysis set. The bleeding pattern was reported using reference periods of 90 days, as stipulated by the World Health Organization (WHO). The bleeding pattern variables to be analysed descriptively by reference period were: number of bleeding/spotting days, number of bleeding days (excluding spotting days), number of spotting-only days, number of bleeding/spotting, spotting-only and bleeding-only episodes.

Bleeding data were reported descriptively in 90 day intervals (last 90 day interval of the first LNG-IUS and consecutive next 90 day intervals of the second LNG-IUS) and relative to the insertion of the second LNG-IUS, with bleeding/spotting reported starting with the day of insertion onward (as day 1, day 2, etc.) and bleeding starting before the subject received the second LNG-IUS (day 1; the day before that was day 2 and so on).

In addition, each woman was categorized separately for each refer-
ce period as follows: no bleeding and spotting during a reference

eriod, no bleeding but 1–9 days of spotting during a 90 day reference period, and >9 days spotting or any bleeding days during a 90 day reference period.

The evaluation by the investigator of the removal/insertion pro-

cedure was to be analysed descriptively, as was the women’s evalua-
tion of pain during the removal procedure and during the insertion.

Reasons for discontinuation were to be documented thoroughly
and tabulated by specific reason. The cumulative continuation rate
for time to removal was to be calculated using the Kaplan–Meier
method, showing estimates at 3 and 12 months after insertion.

The Pearl Index was to be calculated for non-sterilized women only
and separately for women ≤40 years and >40 years on insertion of
the second LNG-IUS. The Pearl Index and the corresponding two-
sided 95% confidence interval (CI) were to be calculated according
to the European Medicines Agency ‘Guideline on clinical investigation
of steroid contraceptives in women’ (European Medicines Agency,
2009). AEs were recorded from insertion of the second LNG-IUS
(or from the administration of the pretreatment in the substudy), coded using an internationally recognized dictionary (MedDRA) and analysed.

**Results**

**Demographic characteristics**

The demographic data are shown in Table I. Most subjects (77.9%) had had a post-menstrual insertion of their first LNG-IUS, while 18.6% had had a post-partum insertion or other (3.5%) insertion timing. Most women were using the LNG-IUS predominantly for con-

traception. The baseline characteristics and the baseline bleeding

pattern of the 155 subjects using the LNG-IUS for contraception

<table>
<thead>
<tr>
<th>Procedure</th>
<th>n = 115</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Removal of the first LNG-IUS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Easy</td>
<td>111</td>
<td>96.5</td>
</tr>
<tr>
<td>Difficult</td>
<td>4</td>
<td>3.5</td>
</tr>
<tr>
<td>Pain during removal of the first LNG-IUS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>65</td>
<td>56.5</td>
</tr>
<tr>
<td>Mild</td>
<td>37</td>
<td>32.2</td>
</tr>
<tr>
<td>Moderate</td>
<td>11</td>
<td>9.6</td>
</tr>
<tr>
<td>Severe</td>
<td>2</td>
<td>1.7</td>
</tr>
<tr>
<td>Insertion of the second LNG-IUS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Easy</td>
<td>100</td>
<td>87</td>
</tr>
<tr>
<td>Difficult</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Pain during insertion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>23</td>
<td>20.0</td>
</tr>
<tr>
<td>Mild</td>
<td>48</td>
<td>41.7</td>
</tr>
<tr>
<td>Moderate</td>
<td>36</td>
<td>31.3</td>
</tr>
<tr>
<td>Severe</td>
<td>8</td>
<td>7.0</td>
</tr>
<tr>
<td>Dilatation</td>
<td>8</td>
<td>7.0</td>
</tr>
<tr>
<td>Before insertion</td>
<td>5</td>
<td>4.3</td>
</tr>
<tr>
<td>During insertion</td>
<td>3</td>
<td>2.6</td>
</tr>
<tr>
<td>Local anesthesia administered</td>
<td>2</td>
<td>1.7</td>
</tr>
<tr>
<td>Before insertion</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>During insertion</td>
<td>2</td>
<td>1.7</td>
</tr>
<tr>
<td>Analgesics given</td>
<td>11</td>
<td>9.6</td>
</tr>
<tr>
<td>Before insertion</td>
<td>11</td>
<td>9.6</td>
</tr>
<tr>
<td>During insertion</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Ease of the procedure as assessed by the physician and pain experienced by the patient (n = 115) are shown, as well as the use of facilitating measures during insertion. These data pertain only to subjects not belonging to the misoprostol substudy (Fig 1).
and of the 49 subjects using it for the treatment of menorrhagia were similar (data not shown).

Continuation rate and reasons for discontinuation

Of the 234 subjects screened, 204 (87%) entered the study (Fig. 1). Of the 204 subjects, 12 (5.9%) discontinued the study (Fig. 1): 5 due to AEs and 7 due to other reasons (including 2 consent withdrawals, 1 protocol deviation, 2 lost to follow-up and 2 others).

The Kaplan–Meier estimate for time to removal of the second LNG-IUS was 0.98 at month 3 and 0.94 at month 12. The reasons for discontinuation due to AEs included: total expulsion, migraine, increased bleeding, endometritis and one case with several AEs (each in one subject, 0.5%). These AEs were assessed by the investigator as related to the LNG-IUS, with the exception of the subject with migraine, which was assessed as not related.

No discontinuations due to pregnancy, perforation or pelvic inflammatory disease occurred. Thus, the Pearl Index was 0.0 during the study (upper limit of the two-sided 95% CI = 3.1 in the subgroup of women who were ≥40 years at screening and upper limit of the two-sided 95% CI = 4.5 in the subgroup of women who were >40 years at screening).

Removal of the first and insertion of the second LNG-IUS

Results of the removal and insertion procedure, as assessed by the women and the physicians are shown in Table II. Both removal and insertion of the LNG-IUS were considered easy in the majority of the cases. Also, the procedures were well tolerated by the subjects, with 88.7 and 61.7% reporting no or mild pain during removal and insertion, respectively. Cervical dilatation was performed and analgesics administered in less than 10% of subjects.

Patterns of bleeding

A low number of bleeding and spotting days were observed during the study (Fig. 2). The median number of bleeding-only days was 0 in all 90 day reference periods except for the reference period starting on the day of insertion of the second LNG-IUS. The median number of spotting-only days varied between 3 and 6 per reference period (Fig. 2).

There was a slight increase in the median number of days of bleeding (1 day) and spotting (1 day) during the reference period starting on the day of the IUS replacement. When the bleeding/spotting was analysed separately for the 7 days preceding and following the IUS replacement, this increase was found to occur during the latter period, and was therefore judged to be due to the removal/insertion procedures.

The median number of bleeding/spotting episodes after insertion of the second LNG-IUS by 90 day reference periods for the reference periods 1, 2, 3 and 4 were 2.0 (25 and 75 percentiles 1.0 and 3.0), 2.0 (0.0 and 3.0), 2.0 (0.0 and 3.0) and 1.0 (0.0 and 3.0), respectively.

The median length of bleeding/spotting episodes after insertion of the second LNG-IUS for reference periods 1, 2, 3 and 4 were 4.0 days (2.5 and 5.0 days [25 and 75 percentiles]), 3.5 (2.0 and 5.0), 3.0 (2.0 and 4.5) and 3.0 (2.1 and 4.9), respectively.

The bleeding patterns were classified into three categories—no bleeding or spotting (i.e. amenorrhea), no bleeding and 1–9 days of spotting, and any bleeding or >9 days of spotting during the reference period. When the last reference period of the first LNG-IUS and the fourth reference period of the second LNG-IUS were compared, the proportion of subjects with amenorrhea increased from 29.8 to 33.3% and spotting-only from 22.2 to 30.6% during the first year of the second LNG-IUS use, whereas the proportion of subjects with any bleeding or >9 spotting-only days decreased form 48.0 to 36.1% (Fig. 3).

When the subjects belonging to each above-mentioned bleeding category at the end of the first LNG-IUS use were followed up during the first year of the second LNG-IUS use, women who were amenorrhoeic were found to maintain their amenorrhea in median (Fig. 4). In the other bleeding categories the median number of spotting/bleeding days decreased (Fig. 4). The most pronounced decrease in median was seen among women reporting spotting for more than 9 days or any bleeding during the first LNG-IUS (Fig. 4).

Safety

AEs (regardless of causality) occurred in 134 subjects (65.7%) during the study. The most frequently reported AEs by preferred term were: headache (19 women; 9.3%), sinusitis (12 women; 5.9%),

Figure 2  Bleeding pattern before and after the exchange from the first to the second LNG-IUS. Median number of bleeding or spotting days (black), bleeding only days (dark grey) and spotting only days (light grey), together with 25 and 75 percentiles (error bars) per 90 day reference periods is shown. Reference period 1 indicates the last 90 days of the first LNG-IUS, and reference periods 1–4 the 90 day reference periods starting from the day of insertion of the second LNG-IUS (arrow).
influenza and upper abdominal pain (each in 10 women; 4.9%). All other terms were reported in fewer than 10 women (data not shown). Table III lists the AEs classified by the investigators as possibly, probably or definitely related to the LNG-IUS, reported by altogether 48 of 204 subjects (i.e. 23.5%). These did not include any SAEs.

**Discussion**

In the present study we find that removal and replacement of the LNG-IUS following approximately 5 years of use was well tolerated by the woman and regarded as easy by the physician in the majority of the cases. In comparison with the first LNG-IUS, uterine bleeding diminished even further during the first year of use of the second LNG-IUS. Moreover, no pregnancies and only once case of expulsion of the LNG-IUS were noted.

The present study is the first prospective multicentre trial evaluating the removal and replacement, and the use of the second consecutive LNG-IUS.
Consecutive LNG-IUS use

LNG-IUS. The study was performed in four European countries with all very similar results. As only women who had used successfully their first LNG-IUS and opted for continuation with a second LNG-IUS were included, the results pertain to a highly selected population. However, this study design closely mimics the clinical setting of continued use of the LNG-IUS.

Bleeding pattern during the first year of use of the second LNG-IUS was the main outcome measure of the study. Approximately 30% of women were amenorrhoeic at the end of the first 5-year segment of LNG-IUS use, and this proportion increased slightly by the end of the first year of the second IUS. Further reduction in the number of bleeding/spotting days was also observed in women with spotting only and in those with spotting >9 days or with any bleeding at baseline. The proportion of women in the latter group decreased from 48% at baseline to 36% at the end of the first year of the second LNG-IUS use. Thus, the patterns of bleeding during the use of the previous LNG-IUS predict the patterns of bleeding during the use of the next LNG-IUS. Also, regardless of the bleeding pattern, uterine bleeding and spotting is reduced even further during the use of the second consecutive LNG-IUS.

When 7 days preceding and following replacement of the LNG-IUS were analysed separately, an average of one extra day of bleeding and spotting was due to the insertion procedure. However, in line with the previous Swedish study (Rönnrédag and Odlind, 1999), no period of irregular bleeding or spotting, which is typically seen during the first 3–6 months of the first LNG-IUS use, occurred after immediate replacement of the LNG-IUS. Therefore, to avoid irregular bleeding a new LNG-IUS should be inserted immediately after the old one is removed. This information is of relevance for both clinical practice and counselling of patients.

The removal of the first LNG-IUS and the insertion of the second LNG-IUS were considered easy by the vast majority of physicians, and were well tolerated by the women. As all women included in the study had had a previously successful insertion of the LNG-IUS, this could be considered an expected result. The insertion problems reported in the earlier study did not occur in the present study. This may be due to several factors, including the older patient population and the use of the old tube inserter in the study by Rönnrédag and Odlind, 1999.

The release rate of LNG from the IUS declines from 20 μg/day at the start of the use to 10 μg/day at the end of 5 years of use, which is associated with a gradual decline in the serum levels of LNG (Mirena Product Monograph, 2009). Upon the insertion of a new IUS, the serum LNG levels increase again, resulting in a possibility of ‘de novo’ hormonal side-effects. In this study, hormonal adverse effects were uncommon, the most common of these being breast pain/tenderness and acne. However, there were no discontinuations that could be classified to be due to hormonal side-effects. Therefore, women contemplating replacement of the LNG-IUS should be informed that due to the slight increase in serum levels of LNG, there is a small possibility of hormonal side effects but that it is very unlikely that these would lead to discontinuation with the IUS.

In conclusion, transition from the first to the second LNG-IUS was uneventful and predictable. The vast majority of the removal and insertion procedures were well tolerated and assessed as easy. Uterine bleeding was reduced even further and patterns of bleeding remained similar to those seen during the use of the previous IUS. These data encourage consecutive use of the LNG-IUS either for contraception or for the treatment of heavy menstrual bleeding.

Acknowledgements

We wish to thank Kurtulus Sahin for his invaluable programming support.

Funding

Financial support from Bayer Schering Pharma AG is gratefully acknowledged.

References


Submitted on September 16, 2009; resubmitted on October 28, 2009; accepted on November 4, 2009.