Predictors of bleeding and user satisfaction during consecutive use of the levonorgestrel-releasing intrauterine system

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BACKGROUND: Consecutive use of the levonorgestrel-releasing intrauterine system (LNG-IUS) is increasing. However, little is known about factors that predict the bleeding during consecutive use. The objective of this study was to analyse the possible factors which may predict the bleeding pattern during the first year of use of a second LNG-IUS.

METHODS: Fertile-aged women (n = 204) who had used their first LNG-IUS for over 4 years and who opted for a second LNG-IUS were recruited. Bleeding data were reported using 90-day reference periods (RPs) starting from the last 90 days of the first LNG-IUS use (baseline), until the end of the first year of the second LNG-IUS (RPs 1–4).

RESULTS: Demographic factors such as age, parity, body mass index, indication of LNG-IUS use or smoking could not be identified as predictors for bleeding and spotting (B/S). Mean (+ SD) number of B/S days was 8.9 (+ 9.1) at baseline. This increased slightly during RP1 and fell to 6.4 (+ 8.1) during RP4. Compared with the mean, women with uterine fibroids or a bleeding pattern of ≥9 days of spotting or any bleeding at RP1 had more B/S days during RP1–4. Although the number of B/S days decreased progressively from RP1 to RP4 in the group with a bleeding pattern of >9 days of spotting or any bleeding at baseline, such a phenomenon was not observed for women with fibroids. The difference for the change in B/S days between women with and without fibroids was statistically significant at RP3 and RP4. A high degree (91.7%) of satisfaction with the bleeding pattern was observed, with amenorrhoeic women being most satisfied.

CONCLUSIONS: Uterine B/S is reduced during consecutive use of the LNG-IUS. Women with uterine fibroids or any bleeding at baseline continued to have more B/S than other women.

Key words: bleeding profile / contraception / heavy menstrual bleeding / LNG-IUS / Mirena

Introduction

The levonorgestrel-releasing intrauterine system (LNG-IUS) was first approved in Finland in 1990 and has been on the market since mid 1990s in most European countries, and since 2001 in the USA. It is currently marketed in more than 120 countries worldwide. The licensed duration of the LNG-IUS use is 5 years. Among European women of reproductive age, ~10% use a long-acting reversible contraceptive method, and the LNG-IUS and Copper IUD are the most popular contraceptives in this class (Heimovitch, 2009). Currently, of all LNG-IUS users, the proportion of women who are using their second device is ~25% in Europe, with rates up to 42% in individual countries (Römer and Lindsberger, 2009).

So far, the limited data available on consecutive use of the LNG-IUS show a high rate, up to 60%, of amenorrhoea (Rönderdag and Odlind, 1999). In line with these observations, we have recently reported data from an international prospective multicentre study on consecutive use of the LNG-IUS (Gemzell-Danielsson et al., 2010). This study showed a high continuation rate and reduction in bleeding or maintenance of amenorrhoea during the first year of the second consecutive LNG-IUS (Gemzell-Danielsson et al., 2010).

The typical bleeding pattern associated with the use of the LNG-IUS includes a period of irregular bleeding/spotting (B/S) during the initial months of use, thereafter the number of B/S days reduces and the rate of amenorrhoea increases, reaching ~20% after 1 year of use (Andersson et al., 1994). Although this bleeding
pattern is well known by many physicians and LNG-IUS users, little is known regarding potential factors that may predict the bleeding pattern during the LNG-IUS use. Knowledge of such factors could aid in counselling potential LNG-IUS users. De Jonge et al. (2007) analysed the predictors of oligomenorrhea at 1 year in first-time users of the LNG-IUS. In their study, a baseline menstrual bleeding duration of <5 days, use of the LNG-IUS for contraception instead of treatment of menorrhagia and absence of menorrhagia before insertion were associated with a higher rate of oligoamenorrhea at 1 year after LNG-IUS insertion. In contrast, age, body mass index (BMI), parity, ovarian reserve parameters and endometrial thickness were not associated with the bleeding pattern. However, so far, there are no published studies on the effect of different factors on the bleeding pattern during consecutive use of the LNG-IUS.

One of the objectives of the present prospective multicentre study was to analyse in depth the possible factors which may predict the bleeding pattern during the first year of use of a second LNG-IUS among fertile-aged women who used their first LNG-IUS either for contraception or for the treatment of heavy menstrual bleeding (HMB)/menorrhagia. The removal and insertion procedure, side effects, continuation rate and reasons for discontinuation during the use of the second LNG-IUS have been estimated and are being reported elsewhere (Gemzell-Danielsson et al., 2010; Heikinheimo et al., 2010).

Materials and Methods

This prospective multicentre study was performed at altogether 17 clinics in Finland, France, Ireland and Sweden between October 2006 and August 2008. Prior to initiation, the study was approved by the appropriate Independent Ethics Committee/Institutional Review Boards (IEC/IRB). In addition, the study was registered at the www.clinical.trials.com (NCT00393198).

The inclusion and exclusion criteria and the study flow have been summarized previously (Gemzell-Danielsson et al., 2010). In brief, 204 fertile-aged women who had been using their first LNG-IUS between 4 years 3 months and 4 years 9 months either for contraception or for the treatment of HMB, and opted for an immediate replacement with a second LNG-IUS were recruited for the study. The women were followed up during last 3 months of the first IUS use (baseline, visit 1), at visit 2 when the first IUS was removed and the second one inserted, and thereafter at 3, 6 and 12 months after the insertion of the second IUS (visits 3–5, respectively).

The primary efficacy variable of the study was the bleeding pattern during the first year of use of the second LNG-IUS. Bleeding data were collected using daily bleeding diaries and reported descriptively using 90 days reference periods (RPs) as stipulated by the World Health Organization starting from the last 90 days of the first LNG-IUS use (baseline) and continuing until the end of the first year of the second LNG-IUS (RPs 1–4). Each woman was categorized based on the bleeding data observed at baseline as I (no bleeding or spotting), II (spotting 1–9 days and no bleeding) and III (spotting >9 days or any bleeding). The B/S during the 7 days before and after the exchange of the IUS was additionally analysed separately to capture any B/S caused by the removal/insertion procedures.

Women were asked to fill out a questionnaire at baseline and at the 12-month visit. The questionnaire contained questions regarding the subjectively experienced menstrual bleeding (increased, unchanged and decreased), as well as the intensity of menstrual pain and premenstrual symptoms (using a four-step Likert-like scale from none to severe) in comparison to that experienced during the last 3 months of the first LNG-IUS use. In addition, the level of agreement (using a five-step Likert-like scale from definitely agree to definitely disagree), with the statements that they were satisfied with their current menstrual pattern, with the absence of bleeding (if applicable) and overall with the LNG-IUS, was collected.

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 (FAS). The influence of several factors on the amount of B/S days was investigated intensively for the following subgroups: age (<30, >30 and ≤40 years), smoker at screening (yes/no), parity (0, 1 and >1 birth), BMI (<25, ≥25 and <30, and ≥30 and <35 kg/m²), fibroids (yes/no), endometrial thickness (<3, >3 and ≤5, and >5 mm) and bleeding category during the last 3 months of the first LNG-IUS use (I, II and III).

The bleeding data were analysed descriptively. In addition, it was statistically tested on the FAS whether, in the single subgroups described above, the means for the change from baseline in B/S days were equal using the F-test. The P-values reported were not adjusted for the four RPs. It should be noted that these statistical tests are all post hoc.

Results

Of the 234 women screened, 204 entered the trial and 191 women completed the first year of use of the second consecutive LNG-IUS. Main indications for using the LNG-IUS were contraception in 155 subjects (76%) or treatment of HMB in 49 subjects (24%). Demographic characteristics were similar in the subjects using the LNG-IUS mainly for contraception or for the treatment of HMB. The number of women with an endometrial thickness of 0–3 mm was 128 (62.7%), >3 to ≤5 mm 60 (29.4%) and >5 mm 16 (7.8%). There were 13 women (6.4%) found to have uterine fibroids with a mean diameter of the largest fibroid of 22.0 (±14.6) mm. Other demographic characteristics have been described previously (Gemzell-Danielsson et al., 2010).

The mean number (±SD) of B/S days increased slightly from 8.9 (±9.1) at RP1 to 11.5 (±10.2) during RP1, and then decreased to 6.4 (±8.1) during RP4 (Gemzell-Danielsson et al., 2010). The increase during RP4 was due to bleeding associated with the insertion procedure. The decrease was mainly due to reduction of spotting-only days, which decreased from 8.1 (±8.1) days during RP1 to 4.6 (±5.8) days during RP4, although the number of bleeding-only days also decreased from 3.4 (±4.7) to 1.8 (±4.0) days, respectively. This change was also evident from self-reported change of B/S (Fig. 1). The proportion of subjects reporting decreased bleeding increased from 22.1% at screening to 39.2% at the end of the first year of the second IUS use (Fig. 1). A total of eight women (4.1%) reported increased bleeding at the end of the study. No apparent common reason for the subjective reporting of increased bleeding was evident from their records.

Analysis of factors influencing bleeding pattern in consecutive use of the LNG-IUS

Analysis of multiple factors (age, parity, BMI, indication of LNG-IUS use, smoking, the presence of uterine fibroids, endometrial thickness and baseline bleeding category) revealed that women with uterine
fibroids or baseline bleeding category III had more B/S days in comparison to women without fibroids or with baseline bleeding in categories I and II (Fig. 2). A slight association between the endometrial thickness and bleeding was also detected: women with an endometrial thickness of 0–3 mm had 7.9 (+8.1) days of B/S in comparison to 11.3 (+11.2) days seen in women with an endometrial thickness of >5 mm (Fig. 2).

The number of B/S days increased by ~2 days from baseline to RP1 among women who did not have fibroids at the screening, and thereafter remained ~3 days lower than baseline during the observation period (Fig. 3). This decrease was not seen among women with fibroids (Fig. 3). The difference in the change of the number of B/S days between the women with and without fibroids was statistically significant during RP3 (P = 0.032) and RP4 (P = 0.013).

Compared with baseline, the number of B/S days slightly increased at RP1 due to the insertion procedure, and thereafter decreased during RP2–4 across all other subgroups except the subgroup with fibroids (data not shown). The greatest reduction of B/S days was observed in women belonging to the bleeding category III, whose number of B/S days remained at 5.4 days lower at RP4, compared with baseline (data not shown). In the subgroups with different endometrial thickness at baseline, the number of B/S days remained 1.8–3.8 days below the baseline at the end of the observation period (RP4, data not shown). The difference in the change from baseline in B/S days in any of the three groups was not statistically significant.

In addition, the influence of age, parity, BMI, indication of LNG-IUS use and smoking on B/S was assessed. No statistically significant effect for any of these factors on B/S could be observed.

Patient questionnaire results
At screening and at 1 year after the insertion of the second IUS, the women filled out a patient questionnaire concerning their satisfaction with their current bleeding pattern and on the occurrence of premenstrual symptoms as well as dysmenorrhea. There were no marked differences between these time points, both showing a high proportion of satisfaction. A total of 99/108 (91.7%) of women definitely or somewhat agreed with a statement that they were satisfied with their current menstrual pattern (Fig. 4). This proportion increased to 100% among the 86 amenorrhoeic women (Fig. 4).

Concerning the occurrence of dysmenorrhea, 72/108 (66.7%) women reported no dysmenorrhea, whereas 29/108 women (26.9%) reported mild and 7/108 women (6.5%) reported moderate dysmenorrhea at 12 months after insertion of the second LNG-IUS. There were no cases of severe dysmenorrhea. When asked about the occurrence of premenstrual symptoms, 30/108 (27.8%) reported none, 59/108 (54.6%) reported mild, 17/108 (15.7%) reported moderate and 2/108 (1.9%) reported severe symptoms at 12 months.

The overall satisfaction with the LNG-IUS at the 12-month visit was 98.4% (n = 192), with 178 women (92.7%) definitely agreeing and 11 women (5.7%) somewhat agreeing with the statement that they were satisfied with the LNG-IUS at 12 months, whereas 2 women (1.0%) somewhat disagreed and 1 woman (0.5%) definitely disagreed with this statement (data not shown).
Discussion

In the present study, we found that the patterns of bleeding during the use of the first LNG-IUS predict the patterns of bleeding during the use of the second LNG-IUS. Except for the slight increase by a couple of days, due to B/S associated with the insertion procedure, uterine bleeding was reduced even further with the consecutive LNG-IUS, or amenorrhoea was maintained. This is in line with the previous Swedish study (Rönnerdag and Odlind, 1999). It is noteworthy that there was no difference in the number of B/S days by the indication of use of the LNG-IUS. Women with uterine fibroids, and those displaying bleeding category III at baseline, continued to have more B/S than women without fibroids, or women of the bleeding category I or II. However, a trend towards reduced B/S was seen in women with fibroids, suggesting that women with fibroids react differently to consecutive use of the IUS. Even in this group, the difference in the change of B/S days was only 5.6 days at RP4. The difference in the change of the number of B/S days between women with and without fibroids was significant during the latter half of the first year with the second IUS.

Interestingly, factors such as age, parity, BMI, indication of use of the IUS and smoking did not significantly influence the patterns of bleeding in the present study. This is in line with the results from a previous study, which analysed predictors of oligoamenorrhoea in first-time users of the LNG-IUS (De Jonge et al., 2007), with the exception that the use of the LNG-IUS for contraception was associated with higher likelihood of oligoamenorrhoea than the use of the LNG-IUS for the treatment of HMB (De Jonge et al., 2007). An explanation to this discrepancy may be the fact that we studied women who had already used the LNG-IUS successfully for the treatment of HMB for almost 5 years. However, we consider it an important finding that the favourable bleeding pattern continued in second consecutive LNG-IUS users, regardless of indication of use. No apparent explanation was found in the 4% of women who reported an increase in bleeding.

Possible limitations of the study are that some of the subset analyses only included a limited number of women in various subgroups. Furthermore, an overlap between subset groups cannot be excluded. Thus, it is likely that some women with fibroids may also have belonged to bleeding category III.

Endometrial thickness measured at vaginal ultrasound examination at baseline was not associated with the bleeding pattern during the second LNG-IUS use, although women with the lowest endometrial thickness had slightly less B/S days at baseline than women with the highest endometrial thickness. However, the difference in the number of B/S days was small. Across the groups, the change in B/S days during the second LNG-IUS seemed to be similar. In a recent study on the extended use of the LNG-IUS, the endometrial thickness increased and the incidence of amenorrhoea decreased when the use of the LNG-IUS was extended beyond 5 years (Hidalgo et al., 2009). In that study, no association was found between LNG serum levels and bleeding patterns. Although increased endometrial diameter resulted in increased bleeding, it was also observed that despite a very thin endometrium of only a few millimetres, menstrual bleeding was reinstated in many cases. Thus, factors other than endometrial thickness such as the expression of local endometrial factors are more likely to be of significant importance for the individual bleeding patterns.

The mean number of B/S days during the last 90-day period was only 6.4. Even in the subgroups with most B/S days (women with fibroids or with baseline bleeding category III), the number of B/S days remained at a level of 16 days or less per 90-day RP, i.e. at a lower level than that reported typically for oral contraceptive users. This was also reflected in the high degree (>90%) of subject satisfaction with the bleeding pattern at the end of the first year of use of the second LNG-IUS, regardless of baseline bleeding pattern. This study included both women using the LNG-IUS for contraception and women using it for the treatment of HMB. These women could have different objectives and perception when using the LNG-IUS. Thus, although the indication of use did not influence the bleeding pattern, it may have influenced acceptability. Most satisfied were the women reporting amenorrhoea, where the satisfaction rate reached 100%.

In conclusion, B/S was reduced during consecutive use of the LNG-IUS. An analysis of multiple factors which may be associated with bleeding revealed that the women with uterine fibroids and those with any bleeding or prolonged spotting episodes at baseline continued to have more B/S also during the use of the second LNG-IUS. In the uterine fibroids group, the number of B/S days did not decrease, whereas for those with bleeding or spotting at baseline, the number of B/S days was reduced during the first year of use of the second LNG-IUS. Irrespective of the baseline bleeding pattern, a high degree of satisfaction was observed at the end of the observation period.

Authors’ roles

P.I. initiated the study. O.H. and K.G.-D. were principal investigators for the trial in Finland and Sweden and gave input on study design. M.K. was responsible for the statistical analysis and gave input on the manuscript writing. O.H., P.I., M.K. and K.G.-D. processed and analysed the data and wrote the manuscript.

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