

A Canadian, Multicentre Study Comparing the Efficacy of a Levonorgestrel-releasing Intrauterine System to an Oral Contraceptive in Women With Idiopathic Menorrhagia

Jan Endrikat, MD, PhD,^{1,2} Heather Shapiro, MD, FRCRC,³ Eeva Lukkari-Lax, MD,⁴ Michael Kunz, PhD,⁵ Werner Schmidt, MD, PhD,² Michel Fortier, MD⁶

¹Bayer Inc., Toronto ON

²Universitätsklinik des Saarlandes, Frauenklinik, Germany

³University of Toronto, Mount Sinai Hospital, Toronto ON

⁴Bayer Schering Pharma Oy, Espoo, Finland

⁵Bayer Schering Pharma AG, Berlin, Germany

⁶Clinique de Recherche en Santé des Femmes, Obstetrics and Gynecology, Quebec City QC

Abstract

Objectives: To evaluate the efficacy of a levonorgestrel-releasing intrauterine system (LNG-IUS) compared with a combined oral contraceptive containing 1 mg norethindrone acetate and 20 µg ethinyl estradiol (OC1/20) in reducing menstrual blood loss (MBL) in women with idiopathic menorrhagia.

Methods: A prospective, randomized, open-label study was conducted in nine centres in Canada. Healthy women over 30 years of age suffering from idiopathic menorrhagia were treated either with LNG-IUS (n = 20) or with OC1/20 (n = 19) over 12 months. The primary endpoint was the change in MBL from baseline to 12 months. Secondary endpoints included treatment success (defined as a MBL score < 100 after 12 months), hemoglobin levels, and the menorrhagia severity score.

Results: In both treatment groups, MBL decreased significantly from baseline to 12 months ($P < 0.001$). For the primary endpoint, the MBL score decreased significantly more in the LNG-IUS group (median from 228 to 13, mean percent change -83%) compared to the OC1/20 group (median from 290 to 72; mean percent change -68%) ($P = 0.002$) after 12 months.

In the LNG-IUS group, 80% of subjects had treatment success compared with 36.8% in the OC1/20 group ($P < 0.009$).

Both treatments increased hemoglobin concentrations significantly between baseline and 12 months. The menorrhagia severity score was consistently lower in the LNG-IUS group at all study time points and was significantly lower ($P = 0.045$) at six months. Both treatments were well tolerated.

Key Words: Levonorgestrel-releasing intrauterine system, idiopathic menorrhagia, oral contraceptive

Competing Interests: see Acknowledgements.

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Conclusion: Both the LNG-IUS and the combined oral contraceptive effectively decreased menstrual blood loss in women with idiopathic menorrhagia. The overall clinical benefit was more pronounced with LNG-IUS than with OC1/20.

Résumé

Objectifs : Évaluer l'efficacité d'un système intra-utérin à libération de lévonorgestrel (SIU-LNG), par comparaison avec un contraceptif oral combiné contenant 1 mg d'acétate de noréthindrone et 20 µg d'éthinylestradiol (CO1/20), en ce qui concerne la diminution de la perte de sang menstruel (PSM) chez les femmes qui présentent une ménorragie idiopathique.

Méthodes : Une étude ouverte, randomisée et prospective a été menée dans neuf centres au Canada. Les femmes de plus de 30 ans présentant une ménorragie idiopathique ont été traitées au moyen d'un SIU-LNG (n = 20) ou d'un CO1/20 (n = 19) sur une période de 12 mois. Le critère d'évaluation principal était la modification de la PSM à 12 mois, par comparaison avec la valeur de départ. Parmi les critères d'évaluation secondaire, on trouvait la réussite du traitement (définie comme un score de PSM < 100 après 12 mois), les taux d'hémoglobine et le score de gravité de la ménorragie.

Résultats : Dans les deux groupes de traitement, la PSM a chuté de façon significative à 12 mois, par comparaison avec la valeur de départ ($P < 0,001$). En ce qui concerne le critère d'évaluation principal, le score de PSM a connu une baisse plus significative dans le groupe SIU-LNG (médiane de 228 à 13, modification moyenne en pourcentage -83 %) que dans le groupe CO1/20 (médiane de 290 à 72; modification moyenne en pourcentage -68 %) ($P = 0,002$) après 12 mois.

Dans le groupe SIU-LNG, le traitement s'est avéré réussi chez 80 % des sujets, par comparaison avec 36,8 % dans le groupe CO1/20 ($P < 0,009$).

Les deux traitements ont entraîné une hausse significative des concentrations en hémoglobine à 12 mois, par comparaison avec la valeur de départ. Le score de gravité de la ménorragie était

régulièrement plus faible dans le groupe SIU-LNG à tous les moments temporels de l'étude et était considérablement plus faible ($P = 0,045$) à six mois. Les deux traitements ont été bien tolérés.

Conclusion : Tant le SIU-LNG que le contraceptif oral combiné sont parvenus à diminuer de façon efficace la perte de sang menstruel chez les femmes présentant une ménorragie idiopathique. L'avantage clinique global était plus prononcé dans le cas du SIU-LNG que dans celui du CO1/20.

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INTRODUCTION

Idiopathic menorrhagia is characterized by chronic heavy menstrual bleeding (≥ 80 mL per menstrual period)¹ without identifiable pathology that often leads to anemia and significant reduction in quality of life.²

Besides surgical therapies (endometrial ablation, hysterectomy), the currently available medical treatments for idiopathic menorrhagia include non-steroidal anti-inflammatory drugs (e.g., mefenamic acid), antifibrinolytics (e.g., tranexamic acid), and hormones (e.g., danazol, oral contraceptives, progestin-only pills, gonadotropin-releasing hormone agonists). Because oral therapies lack efficacy and have side effects, there is frequent recourse to surgical procedures such as endometrial ablation or hysterectomy. Hence, there is a need to develop alternative treatments that are effective and safe.

The levonorgestrel-releasing intrauterine system (Mirena, Bayer Inc. Canada) is a highly effective contraceptive method. It can also be used as an alternative to the currently available treatments for menorrhagia. Since its introduction, it has been used by more than 9 million women worldwide.³ It delivers up to 20 μ g of LNG to the uterine cavity daily, resulting in reduced endometrial proliferation. This effect leads to a significant reduction (80%–95%) in MBL^{4–9} and, consequently, an increase in hemoglobin levels.⁷ In addition, the local administration of LNG produces minor systemic hormonal effect^{5,7,10,11} and is therefore better tolerated than orally administered LNG. The LNG-IUS is effective for up to five years after insertion, allowing for reversible, long-term treatment without compliance issues.

To date, the clinical effect of LNG-IUS on MBL has been compared to endometrial resection,^{8,12} flubiprofen or

tranexamic acid,¹³ mefenamic acid,⁹ and norethisterone.⁵ The primary aim of this study was to evaluate the efficacy of the LNG-IUS compared with a combined oral contraceptive containing 1 mg norethindrone acetate and 20 μ g ethinyl estradiol in the treatment of idiopathic menorrhagia.

MATERIALS AND METHODS

We conducted a prospective, randomized, open-label, 12-month study at nine centres in Canada. Participants were otherwise healthy women, aged ≥ 30 at entry, with a diagnosis of idiopathic menorrhagia (assessed by a MBL score ≥ 100 on the pictorial chart for 2 consecutive cycles) and with a normal or only slightly enlarged uterus.

Primary exclusion criteria were the contraindications for LNG-US and combined oral contraceptive use. Further exclusion criteria included metabolic and endocrine diseases, diagnostically unclassified genital bleeding, and a history of liver or vascular diseases. In addition, concomitant use of medications that could influence the study objectives, including sex steroids, any treatment for menorrhagia (including tranexamic acid and non-steroidal anti-inflammatory drugs), drugs that could affect bleeding patterns (platelet aggregation inhibitors, anticoagulants) and drugs known to induce or to inhibit liver enzymes was not permitted. Women who had intramural or subserous fibroids of mean diameter ≥ 4 cm or submucous fibroids, adenomyosis, or endometrial abnormalities (e.g., polyps or hyperplasia, verified by saline infusion sonography or hysteroscopy) or who were perimenopausal (as evidenced by serum FSH levels > 50 IU/L and serum estradiol levels < 100 pmol/L) were also excluded.

At screening, all women underwent a thorough medical and gynaecological examination, including a Papanicolaou test and a pregnancy test. After giving informed consent, participating subjects were randomized, in order of arrival at the treatment centre, to treatment using either the LNG-IUS or a combined oral contraceptive.

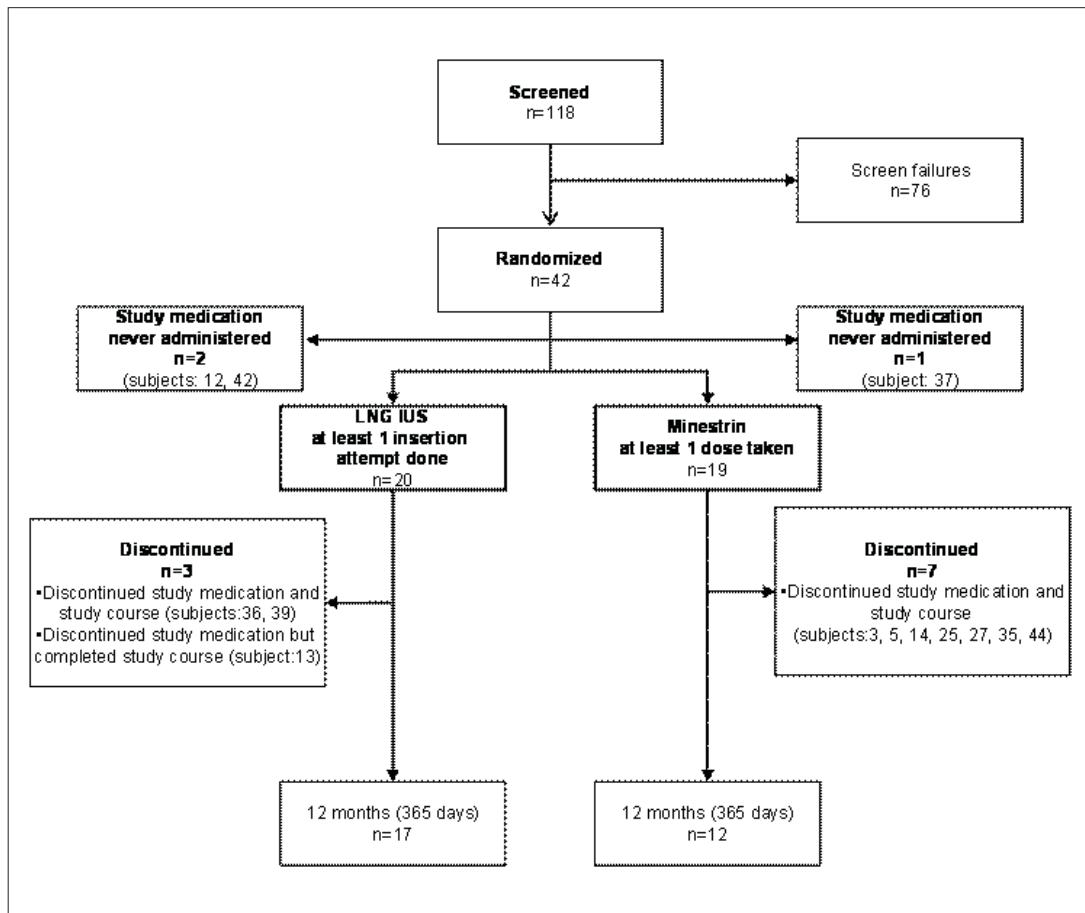
The LNG-IUS (Mirena, Bayer Inc. Canada) comprises a T-shaped polyethylene frame with a hormone cylinder around the vertical arm. The total amount of LNG in the system is 52 mg. The system releases up to 20 μ g LNG per 24 hours. For women randomized to undergo treatment with the LNG-IUS, it was inserted into the uterus by a physician within seven days of the start of the last menstrual period for a treatment period of 12 months.

Women randomized to treatment with a combined oral contraceptive (OC1/20) used a preparation containing norethindrone acetate and ethinyl estradiol (Minestrin, Parke-Davis Canada) and took one tablet daily over 12 months. In each 28-tablet blister pack, the first 21 tablets

ABBREVIATIONS

FAS	full analysis set
IM	idiopathic menorrhagia
LNG-IUS	levonorgestrel-releasing intrauterine system
MBL	menstrual blood loss

Figure 1. Flow of participants



(days 1 to 21) contained 1 mg norethindrone acetate and 20 µg ethinyl estradiol, and the last 7 tablets (days 22 to 28) contained placebo.

Both treatments were commercially available in Canada for contraception.

The primary outcome measure was MBL, and the secondary measures were treatment success (i.e., clinical outcome), hemoglobin concentration, and the menorrhagia severity score (to evaluate the effect of treatment on quality of life). In order to quantify MBL, we applied the pictorial blood loss assessment chart published by Higham et al.¹⁴ This validated graphical scoring system was completed by the patient and served as the basis for MBL score calculation. The MBL score was evaluated during the two month screening phase in order to identify eligible patients, i.e., patients with an MBL score ≥ 100 in both cycles (a score ≥ 100 corresponds to blood loss per menstrual period of ≥ 80 mL, which is the definition of idiopathic menorrhagia).^{1,14} The mean score of these two months was

used for the baseline value. Thereafter, patients completed the pictorial charts for six consecutive months.

The pictorial blood loss assessment chart consisted of a series of diagrams representing lightly, moderately, and heavily soiled tampons or pads. Each time a sanitary pad or tampon was discarded, the patient recorded her perceived blood loss on the diagram chart. Finally, the investigator or a designated representative calculated the scores according to Higham et al.¹⁴ The number of soiled tampons or pads, the size of the blood spots and clots were included in the calculation. The scores were totalled for the duration of the last bleeding period prior to day 90 (assessment after 3 months) and day 180 (assessment after 6 months). A bleeding period was defined as an episode of bleeding or spotting, preceded and followed by at least two days without bleeding, occurring within a 45-day window prior to the assessment days (day 90 and day 180). In order to optimize the accuracy of the pictorial chart assessment, pads and tampons were supplied by the sponsor to ensure uniform size and absorbency level.

Demographic and baseline characteristics (full analysis set)		
	LNG-IUS (n = 20)	OC1/20 (n = 19)
Age (years)	41.8 ± 4.3	42.4 ± 4.4
Height (cm)	164.4 ± 5.0	163.4 ± 7.6
Bodyweight (kg)	65.6 ± 6.8	60.2 ± 5.5
BMI (kg/m ²)	24.3 ± 1.9	22.6 ± 2.3
Number of births		
0	3 (15.0%)	3 (15.8%)
1	6 (30.0%)	4 (21.1%)
2	6 (30.0%)	10 (52.6%)
≥ 3	5 (25.0%)	2 (10.5%)
Patient not taking iron supplements	12 (60%)	9 (47%)
Time since start of menorrhagia (years)	10.0 ± 8.23	6.1 ± 4.4

Data are expressed as means ± SD or n (%) of women.

Treatment success (i.e., clinical outcome) was defined as a MBL score < 100 at 12 months, and treatment failure was recorded if the MBL score was ≥ 100 or if the treatment was discontinued.

Hemoglobin concentration was measured at baseline and at three-month intervals up to 12 months or at the premature discontinuation visit. Local laboratories were responsible for blood sampling and analyses.

We assessed the menorrhagia severity score using the condition specific questionnaire by Ruta et al.¹⁵ Women completed this questionnaire at baseline and at three-month intervals up to 12 months. The response values ranged from 0 to 5. The responses to all the questions were totalled and divided by the total possible score (which was 42 if all questions were answered). This value was expressed as a percentage, producing a score between 0% (least severe) and 100% (most severe).

The primary efficacy variable was the change in MBL score from baseline to 12 months. Secondary efficacy variables included treatment success (i.e., clinical outcome), as defined by an MBL score < 100 after 12 months, hemoglobin concentrations, and the menorrhagia severity score at baseline and at three-month intervals over 12 months.

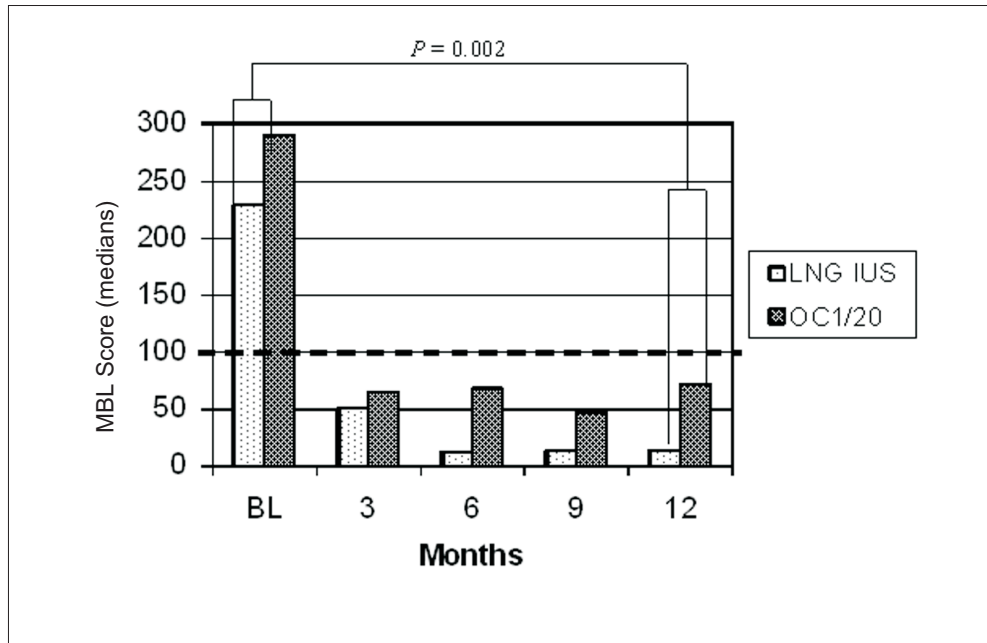
Adverse events, vital signs, weight, routine safety laboratory parameters, and results of physical and gynaecological examinations (including pelvic and breast examination) were recorded during the study. In addition, a Papanicolaou smear and an endometrial biopsy were taken before and after the study.

The primary population of interest was the FAS population, which consisted of all patients who had taken at least one dose of study medication and reported at least one efficacy measure or valid diary entry after randomization. The safety population consisted of all patients who took at least one dose of study medication and had post-baseline safety data collected. All patients who completed the study without a major protocol violation were included in the per protocol set.

The MBL scores were summarized by treatment group for absolute values and for change from baseline values. Results are reported for the FAS, as the results for the per protocol set confirmed the results obtained on the FAS. Inferential statistical analysis was carried out only for the FAS population.

The first model of choice for the primary efficacy variable was an analysis of covariance (ANCOVA model) with the factors treatment and baseline value. However, as the normality assumption was rejected by the Shapiro-Wilk test in the LNG-IUS treatment group ($P < 0.001$), a rank ANCOVA was performed. The conditions for this change to non-parametric analysis had been described in the statistical analysis plan. The parametric model did not show a statistically significant treatment difference. An analysis using last observation carried forward was performed to assess the robustness of the findings. The difference in treatment means and a 95% confidence interval were estimated from the ANCOVA model. Treatment success (yes/no) was investigated using the Fisher exact test. P values of < 0.05 were considered significant.

Figure 2. Median MBL scores at baseline and after 3, 6, 9, and 12 months. Primary endpoint: change in MBL score from baseline to 12 months. FAS population.



The study protocol was in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization—Good Clinical Practice Guidelines of January 17, 1997. Ethics committees or institutional review boards of each centre reviewed and gave approval for the protocol before the study started. All women gave their informed consent before participation in the study.

RESULTS

We screened a total of 118 women and randomized 42 to treatment. Of these, 20 were assigned to LNG-IUS and 19 to OC1/20 (FAS). Following randomization, three women did not receive treatment and were therefore excluded from the FAS. Seventeen women treated with LNG-IUS and 12 women treated with OC1/20 completed the 12-month study (Figure 1). The demographic and baseline characteristics were well matched in both treatment groups (Table).

MBL scores declined sharply during the first three months in both treatment groups. Both treatments significantly decreased the mean MBL over time from baseline to 12 months ($P < 0.001$ for the change from baseline in each treatment group separately). In the LNG-IUS group, the median MBL score decreased from 228 at baseline to 13 at 12 months (mean change -83%), and in the OC1/20 group from a median of 290 to 72 (mean change -68%). The decrease was significantly larger in the LNG-IUS group

than in the OC1/20 group ($P = 0.002$; estimate for median difference -62 ; 95% CI -89 to -18) (Figure 2).

In the LNG-IUS group, 16 of the 20 subjects (80.0%) showed treatment success, and in the OC1/20 group 7 of the 19 subjects (36.8%) achieved treatment success. This difference was statistically significant ($P < 0.009$).

Both treatments increased mean hemoglobin concentrations significantly from baseline to 12 months ($P < 0.001$). In the LNG-IUS group the mean hemoglobin concentration increased from 126 g/L at baseline to 134 g/L at 12 months (baseline adjusted mean change $+8.6$ g/L), and in the OC1/20 group from 125 g/L to 136 g/L (baseline adjusted mean change $+9.6$ g/L). There was no significant difference between treatment groups in change in hemoglobin concentration from baseline to 12 months ($P = 0.711$; estimate for mean difference -0.99 g/L; 95% CI -6.43 to 4.45) (Figure 3).

Hemoglobin levels were also analyzed in the sub-population of subjects who had not used iron supplements during the study. The results were similar to the results of the whole population (data not shown).

At all study time points the mean menorrhagia severity score was lower (reflecting higher quality of life) in subjects treated with LNG-IUS compared to subjects treated with OC1/20. The menorrhagia severity score was significantly lower ($P = 0.045$, unadjusted) in the LNG-IUS group at 6 months (estimate for difference -6.37 ; 95% CI -12.61 to -0.14)

Figure 3. Mean Hb levels (g/L) at baseline and after 3, 6, 9, and 12 months. Secondary endpoint: Change in Hb score from baseline to month 12 tested. FAS population

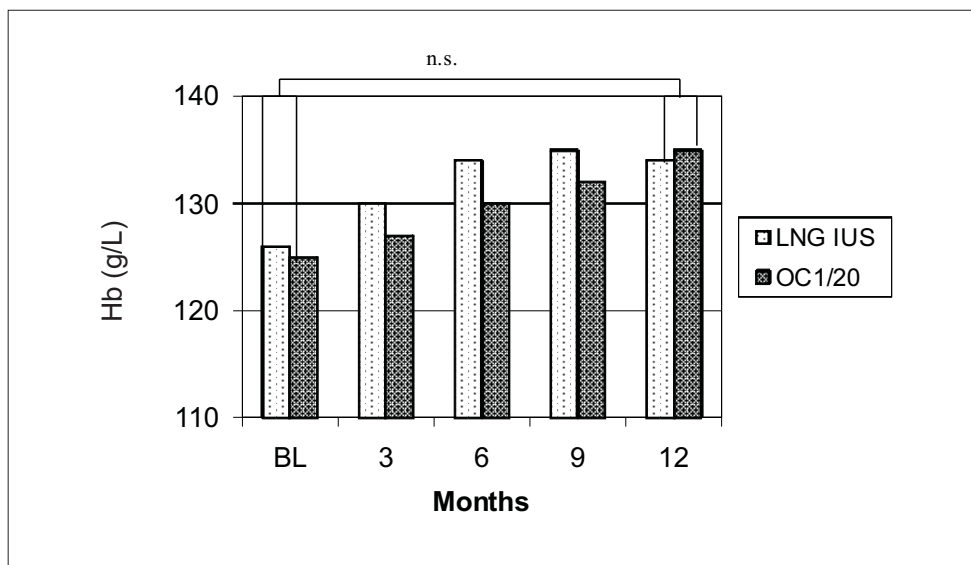
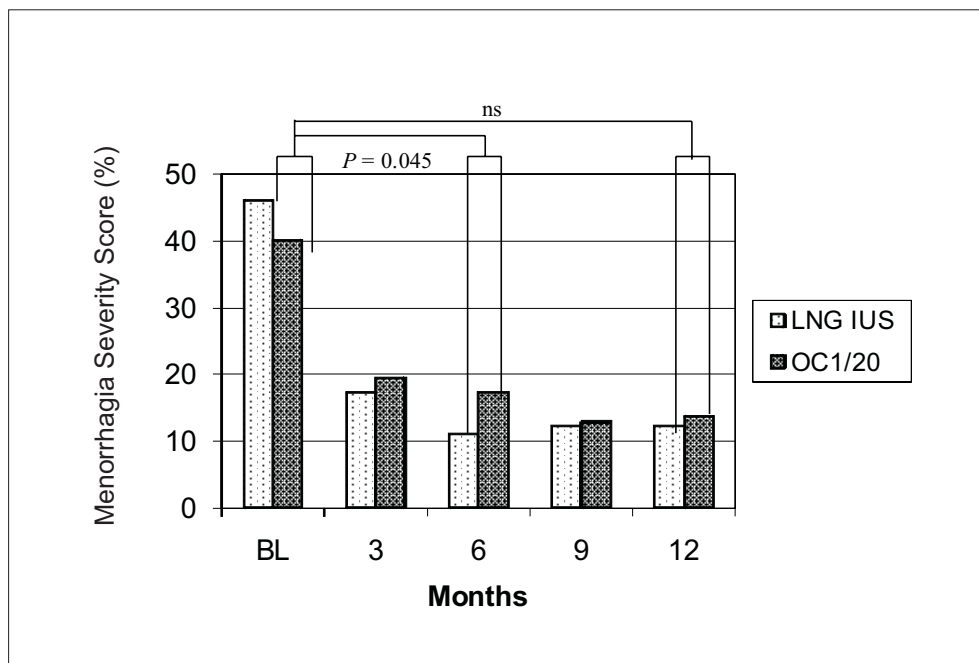


Figure 4. Mean menorrhagia severity score (%) at baseline and after 3, 6, 9, and 12 months. Secondary endpoint: score from baseline to month 6 and 12 tested. FAS population



(Figure 4), while at the other time points no significant difference was seen.

Both treatments were well tolerated. One subject in the LNG-IUS, and five in the OC1/20 group discontinued the study because of adverse events. The most frequent reasons for study discontinuation were intermenstrual bleeding, menstrual disorder, and headache. One subject in the LNG-IUS group reported an inguinal hernia, which was considered a non-treatment related serious adverse event. No deaths occurred during the study.

Routine safety parameters, including vital signs, weight, physical and gynaecological examination, cervical smear, and endometrial biopsy, did not suggest any significant influence for either study medication.

DISCUSSION

This study is the first reported head-to-head comparison between LNG-IUS and a combined oral contraceptive in the management of idiopathic menorrhagia using the pictorial blood loss assessment chart, an easy and practical

method to quantify menstrual blood loss.¹⁴ Our data provide convincing evidence that the LNG-IUS is an effective method for reducing MBL.

Our findings are in keeping with several previous publications that investigated the therapeutic effect of LNG-IUS on MBL.^{4,5,8–10,12,13,16} In a total of more than 150 women with menorrhagia, the MBL was reduced by 80% to 95% with use of LNG-IUS. Barrington et al. studied 50 women who failed medical treatment for menorrhagia and who were waiting for hysterectomy or transcervical endometrial resection.¹⁶ Forty-one of these women cancelled their surgery after insertion of a LNG-IUS because of the reduction in menstrual blood loss and subsequent achievement of amenorrhea. Xiao et al. were able to show in a group of 34 women that MBL was significantly reduced for up to 36 months.¹⁰

In our study, we identified a reduction in MBL after three months that was similar to published reports (mean reduction with LNG-IUS 83%; with combined oral contraceptive 68%). The effect remained stable during the treatment and observation period of 12 months. While the MBL score was lower for LNG-IUS than for OC1/20 at all time points (Figure 2), we confirmed significant and clinically relevant reductions in MBL at our primary endpoint at 12 months. We also showed a complementary rise in mean hemoglobin concentration in both treatment arms (Figure 3), thus confirming the results of other studies.¹⁰

As a third pillar for evaluating the therapeutic effect, we used a patient-administered questionnaire¹⁵ to determine the menorrhagia severity score. This subjective tool to measure health status (quality of life) also showed benefit in both treatment groups, with a slightly more pronounced effect for LNG-IUS at all time points.

Excessive menstrual blood loss is an increasingly common health problem¹⁷; many women with heavy menstrual bleeding consult health care professionals in primary care, and this condition is a common reason for referral to a specialist.⁴ Oral contraceptives are widely used as an effective, easy to use treatment option. The LNG-IUS offers another effective, reversible^{8,18} and cost-effective¹⁹ treatment option, with two major advantages: first, the local administration of LNG produces minor systemic hormonal effect,^{5,7,10,11} which is therefore better tolerated than orally administered sex steroids. Second, the LNG-IUS can be inserted for a period of five years, allowing effective long-term contraception for which compliance is not an issue. Women with IM, regardless of age, could thus be treated until menopause, without being subjected to any surgery.

In women who may want to conceive, the LNG-IUS can be easily removed and fertility is quickly restored.^{20,21}

CONCLUSION

Both the LNG-IUS and the combined oral contraceptive effectively decrease menstrual blood loss in women with idiopathic menorrhagia. In our study, the overall clinical benefit was more pronounced with LNG-IUS than with the combined oral contraceptive preparation.

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