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Impact of a new levonorgestrel intrauterine system, Levosert®, on heavy menstrual bleeding: results of a one-year randomised controlled trial

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ABSTRACT

Objective To evaluate a new levonorgestrel-releasing intrauterine system (LNG-IUS) called Levosert® for the treatment of heavy menstrual bleeding (HMB) in comparison to the reference product Mirena®.

Methods A multicentre, randomised, controlled trial, in non-menopausal women diagnosed with functional HMB (defined as menstrual blood loss [MBL] ≥ 80 mL) randomised to either Levosert® or Mirena® and followed for up to one year. MBL was evaluated using a validated modified version of the Wyatt pictogram.

Results A total of 280 women were randomised (141 to Levosert® and 139 to Mirena®). During the one-year treatment period, both Levosert® and Mirena® dramatically decreased MBL and increased haemoglobin and ferritin levels. There were no statistically significant differences between Levosert® and Mirena® regarding any of the parameters evaluated during the study. Similar bleeding patterns were observed in both groups. Levosert® was inserted with the same ease as Mirena®. Both treatments were associated with identical expulsion rates and no perforations occurred in either treatment group.

Conclusion Levosert®, a new LNG-IUS designed to release the same daily amount of LNG as Mirena®, is highly effective in the treatment of HMB. No differences were observed between Levosert® and Mirena® regarding all evaluated outcomes, including safety profile.

KEYWORDS Heavy menstrual bleeding; Intrauterine system; Levonorgestrel; Levosert®; Mirena®

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INTRODUCTION

Heavy menstrual bleeding (HMB) affects 10 to 35% of women[1–5]. Treating this disorder may improve a woman's quality of life and may prevent the occurrence of iron deficiency anaemia.

'Normal' levels of menstrual blood loss (MBL) vary between cycles within the same woman, with 40% experiencing a 10 mL difference between cycles[6]. Iron depletion and anaemia occur when menstrual flow regularly amounts to approximately 60 and 120 mL MBL, respectively[7]. HMB is classically defined as blood loss of- or exceeding 80 mL per menstrual cycle[8,9]. The anomaly is the consequence of a variety of functional, non-structural, and structural conditions. Among the latter the main causes are adenomyosis and fibroids (leiomyomata). Non-structural causes refer to coagulopathies and iatrogenic causes[10]. In a substantial proportion of women, the underlying cause of HMB remains unknown and is referred to as functional HMB[11].

Whenever possible, HMB treatment should specifically target its underlying cause. A medical approach should be the first line of treatment[12]. Surgery (endometrial ablation and hysterectomy) is associated with perioperative and long-term surgical risks[13], and does not preserve fertility. Strong evidence indicates that the intrauterine system (IUS), releasing controlled amounts of levonorgestrel (LNG), is an effective medical treatment for HMB and is superior to drugs administered orally such as oral contraceptives, tranexamic acid and non-steroidal anti-inflammatory drugs, whether used alone or in combination[12–16]. The 2005 Cochrane meta-analysis identified ten randomised controlled trials (RCTs) comparing the LNG-IUS with surgery or various oral HMB treatments. The calculated odds ratio (OR) for amenorrhoea was 8.67 (95% confidence interval [CI]: 1.52–49.35) favouring treatment with a LNG-IUS[16].

The LNG-IUS Mirena® (Bayer Healthcare Pharmaceuticals, Germany) was approved for the treatment of HMB more than a decade ago in Europe; the US Food and Drug Administration approved the system for this indication in 2009.

In the present study, the effectiveness for treatment of functional HMB of a new LNG-IUS, called Levosert® (Uteron Pharma Sprl, Liège, Belgium), was compared with the reference IUS Mirena®, during one year of use. Like Mirena®, Levosert® contains

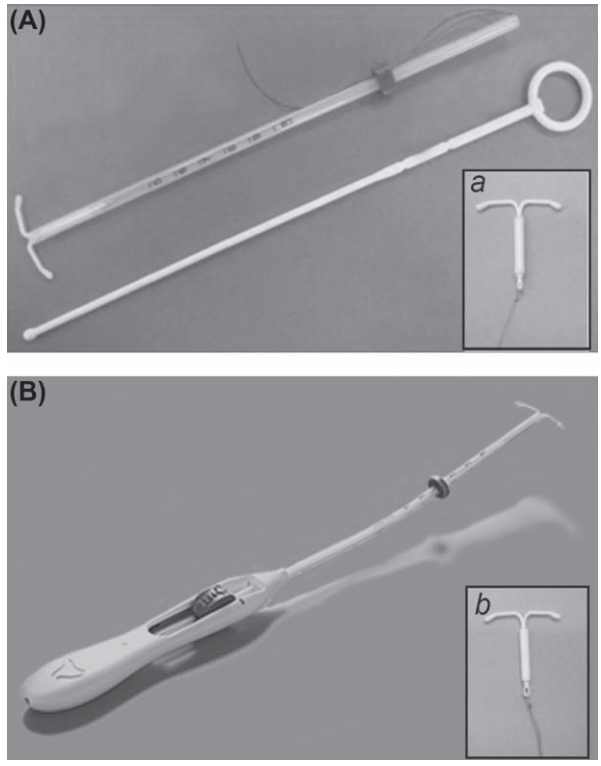

Figure 1 Levosert® and its inserter are depicted in picture (A) and in insert a, respectively. Mirena® and its inserter are shown in picture (B) and in insert b, respectively.

52 mg of LNG in a cylindrical-shaped reservoir mounted on the vertical arm of a T-shaped plastic frame. The reservoir is covered with a membrane controlling the release rate of the progestin, so as to deliver *in utero* the same daily amount of LNG as does Mirena®. Although minute structural differences exist between Mirena® and Levosert® (different shapes of horizontal extremities, thinner plastic vertical arm [Levosert® 1.2 mm, Mirena® 1.5 mm], and smaller inferior loop), the most significant difference pertains to its mode of insertion. Whereas Mirena® is fitted by means of a specific one-handed inserter, the one used for placing a Levosert® is a two-handed cylindrical tube, similar to that used for the Nova-T copper intrauterine device (Cu-IUD). The Levosert® inserter closely resembles the two-handed Mirena® inserter commonly used in France. This difference may have a significant impact, particularly in developing countries where healthcare professionals are more used to placing intrauterine devices with a two-handed inserter and where access to training in other insertion systems is often limited (Figure 1).

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The development of a reliable progestin-releasing IUS for long-term use is complex. Despite multiple attempts since the 1970s, only Mirena® has successfully completed the approval process so far. Difficulties inherent to IUS development (long-term clinical studies, sophisticated technologies, specific pharmacodynamics with local action only) have precluded thus far the launch of other IUSs.

Levosert® development required full clinical investigation of its efficacy in treating HMB and its contraceptive properties. The use of *in vitro* release studies or the demonstration of similar plasma LNG levels between Levosert® and Mirena® users in bioequivalence studies is not sufficient for agencies to consider clinical efficacy. The local mode of action of the LNG-IUS and its pharmacodynamics preclude extrapolation of systemic data to local impact and clinical efficacy. Large clinical trials were therefore required to demonstrate the clinical performance of Levosert®.

In this study, the effect of local LNG release from Levosert® or Mirena® on the MBL is described. The contraceptive efficacy will be described elsewhere.

METHODS

IUS development

Levosert® consists of four parts: a polyethylene T-frame, a polypropylene thread, a reservoir made of a mixture of LNG and polydimethylsiloxane (PDMS), and a PDMS membrane that controls LNG diffusion. A quality by design strategy was developed according to the current state of the art pharmaceutical development guidelines, i.e., ICH Q8(R2)[17]. The 21CFR part 820.30 guideline[18] was used for the development of the T frame, thread and inserter.

The major structural differences between Levosert® and Mirena® concern the T-frame: the buds at the end of the horizontal arms of Levosert® are more flattened and its vertical stem is thinner (diameter: 1.2 mm vs. 1.5 mm for Mirena®). The loop at the end of the vertical stem (width: 1.8 mm vs. 2.4 mm for Mirena®) and the hole in it (length: 0.85 mm and width: 0.6 mm vs. 2.2 mm and 1.3 mm, respectively, for Mirena®) are both smaller. The two intrauterine systems also differ with regard to the composition of the thread which is in polypropylene dyed with phtalocyaninato (2-)copper for Levosert®, and in polyethylene with 1% ferric oxide for Mirena®. None of these differences affects the IUS's performance or the ease of its insertion.

Study design

The study was a multicentre, randomised, parallel group, single-blind clinical trial. Women who met the inclusion- and exclusion criteria were randomised to either Levosert® or to Mirena® in a 1:1 ratio for a duration of up to 12 months. Twelve centres located in Serbia (one centre), Romania (eight centres), and Macedonia (three centres) took part in the trial, which lasted from December 2007 (initiation of recruitment) to January 2010 (completion of the final assessment). It was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization – Good Clinical Practice guidelines. The study protocol was approved by the appropriate Ethics Committees before the study started: in Romania, by the National Ethics Committee for Clinical Study of Drugs at the Medical Sciences Academy; in Serbia, by the Ethics Committees of the Gynaecology and Obstetrics Clinic 'Narodni front', the Clinical Centre of Serbia, the Mother and Child Health Care Institute of Serbia and the Clinical Centre of Vojvodina; and, in Macedonia, by the Ethics Committee of the Faculty of Medicine in Skopje. The trial was registered in the Romanian National Medicinal Agency under EudraCT number 2007-001564-77.

Selection criteria

Women were eligible to enter the trial if they were at least 18 years of age, not pregnant nor planning to become pregnant, not lactating, not menopausal, and had a clinical diagnosis of functional HMB for at least six months prior to screening. Exclusion criteria were: a known or suspected pregnancy; a history of endometrial ablation or curettage during the preceding three months; use of a Cu-IUD or LNG-IUS during the two months prior to screening; current use of other hormonal treatment (sex steroids); endometrial polyps; submucous myomas of any size or intramural or subserous myomas greater than 3 cm; adenomyosis; atypical hyperplasia or carcinoma of the endometrium; an abnormal Pap smear test or other evidence of cervical malignancy; abnormal uterine morphology; ovarian cysts >3 cm; a known or suspected

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hormone-dependent tumour; lower genital tract infection; pelvic inflammatory disease during the past three months; abnormal liver function; renal insufficiency; uncontrolled hypertension; valvular disease (including corrections with prosthetic valves); a body mass index (BMI) >30 kg/m^2, and hypersensitivity to device material and/or LNG.

Women who met these criteria and who signed the written informed consent form were followed for three cycles prior to randomisation, during which their MBL was measured by means of the modified Wyatt pictogram[19]. To ensure the homogeneity of the measurements, all women were given the same sanitary pads (brand: Always® Ultra sensitive normal plus and super plus). For this trial, the pictogram and related digital photos used by Wyatt *et al.* were adapted to Always® sanitary products. The usability and readability of these modified pictogram and related photos were validated before starting the study; validation involved 20 women of various ages and educational backgrounds. Only women with documented HMB (≥ 80 mL) for at least two bleeding episodes were randomised in a 1:1 ratio to either Levosert® or Mirena®. Randomisation was done using a two digit number allocated to the subject based on the sequence of the woman's arrival at the study site. All women with even randomisation numbers received Mirena®, those with odd numbers, Levosert®.

Interventions

The study included two treatment groups: the Levosert® and the Mirena® groups. Both IUSs were inserted within the first seven days of the menstrual cycle, according to the manufacturer's instructions. Participating women were to be followed for the 12-month study period.

Study outcomes

MBL during each menstrual cycle was evaluated using the modified Wyatt pictogram scoring system and recorded on a diary card. To increase the reliability of the measurements, screened women were instructed on how to interpret the modified Wyatt pictogram and had a chance to complete it during the three cycles prior to randomisation. Only, those who successfully completed the pictogram scoring were included.

Endometrial thickness was assessed by trans-vaginal ultrasonography (TVUS) at baseline, and three, ten and twelve months after insertion of the IUS. To this end, the distance between the basal layers of the endometrium covering the anterior and posterior uterine walls (at the echogenic interface between endometrium and myometrium) was measured. To harmonise the data regarding endometrial thickness across the different participating centres, all investigators were trained by an expert in gynaecological ultrasound. Effects of the treatment on MBL were also indirectly assessed by the measurement of haemoglobin and ferritin levels at baseline, and one, three, ten and twelve months after initiation of treatment. A urinary pregnancy test was performed at each visit. Adverse events, concomitant medications and cycle control pattern (menstrual cycle length, days of spotting and bleeding) were recorded in daily diaries.

Statistical analysis

For all statistical calculations SAS® 9.2 (SAS Institute) was used. Based on the magnitude of the individual variability in MBL reduction reported for Mirena®[12] and the documented 10 mL MBL difference between spontaneous cycles within the same woman[6], the limit for claiming the equivalence between Levosert® and Mirena® was defined as ± 20 mL in terms of MBL reduction. Based on a standard deviation of 48.9 mL for the MBL reduction (estimated by simulations based on the results published by Kaunitz *et al.*[12]) and assuming that the true difference between Levosert® and Mirena® in terms of MBL reduction would not exceed 5 mL, it was determined that a sample size of 280 women (140 women in each treatment group) was needed. Equivalent efficacy in terms of reduction of HMB required therefore that the 95% CI for the difference in MBL reduction be within ± 20 mL (SAS® 9.2 Proc power).

All safety and efficacy endpoints were summarised by descriptive statistics (mean, standard deviation, standard error of the mean, and percentage) for continuous data or by frequency tables for ordinal or nominal data.

The two treatment groups were compared at baseline using an independent t-test (SAS® 9.2 Proc ttest) for age, number of deliveries, BMI, MBL, haemoglobin, ferritin and endometrial thickness, and a chi-squared test for the proportion of subjects with iron deficiency anaemia defined by a haemoglobin level <12.0 g/dL and a ferritin level <15 ng/mL. At

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the end of the treatment period, changes from baseline were compared between both treatments for the following outcomes: mean blood loss, haemoglobin, ferritin, and endometrial thickness. The results at baseline and at end-of-study are reported as arithmetic means and standard deviation. For this evaluation, a model of analysis of covariance (ANCOVA) was used, with the treatment as fixed effect and the baseline value as continuous covariate (using SAS® 9.2 Proc mixed). These outcomes were primarily assessed taking into account the intention-to-treat (ITT) principle with a last-observation-carried-forward (LOCF) imputation of the missing values, and secondarily using a per-protocol (PP) analysis without imputation of the missing values. To reflect the statistical inference achieved, the changes from baseline are presented as least-squares means, i.e. means adjusted for the different factors included in the statistical model. The treatments have been statistically compared using an analysis of covariance (ANCOVA) with the baseline value added as a continuous covariate. The least-squares means on the change from baseline were adjusted for the effect due to the baseline by SAS® 9.2 Proc mixed.

RESULTS

Study population

A total of 341 women were screened and, of these, 280 were randomly allocated to one of the two treatment groups: 142 to the Levosert® group and 138 to the Mirena® group; they constituted the ITT population. Of these, 126 and 121 participants completed the treatment year in the Levosert® and the Mirena® groups, respectively. At the end of the study, 219 of them had no major protocol deviations and were included in the PP population, i.e., 113 in the Levosert® group and 106 in the Mirena® group. All 280 randomised women were included in the safety population. However, due to an inversion of treatment, one woman randomised to Levosert® actually received Mirena®; as a result thereof the safety population includes 141 women treated with Levosert® and 139 treated with Mirena® (Figure 2). No statistically significant differences were found between the baseline characteristics of the two groups for age, BMI, parity, MBL, haemoglobin and ferritin levels, endometrial thickness and incidence of iron deficiency anaemia (Table 1). All subjects enrolled were Caucasian.

Menstrual blood loss

Table 2 displays the changes observed in MBL and related parameters (endometrial thickness, haemoglobin and ferritin levels) after one year of treatment. Results are compared to those obtained with the reference product, Mirena®, in both ITT and PP populations.

Levosert®- as well as Mirena® users experienced a consequent and similar ($p > 0.1$) reduction in MBL (-142.3 and -146.4 mL, respectively, in the ITT population; -150.9 and -151.2 mL, respectively, in the PP population) after one year of use. Figure 3 shows the reduction in MBL throughout the treatment period in the ITT population. Most of the decrease in MBL was reached after three months (weeks 13–14) of treatment; it was almost completely achieved after nine months (week 38) of treatment and remained stable thereafter.

Haemoglobin and ferritin levels

Table 2 shows the changes in ferritin and haemoglobin levels from baseline to the end of the treatment. These data, as recorded at each visit, are also represented in Figures 4 and 5.

Simultaneously to the reduction in MBL, in the ITT population, mean ferritin levels increased by 16.0 μg/L in the Levosert® group and by 15.5 μg/L in the Mirena® group. A more pronounced increase was observed in the PP population ($+17.7$ μg/L and $+18.2$ μg/L in the Levosert® and the Mirena® groups, respectively).

Due to the greater availability in iron, haemoglobin levels rose in both groups by 0.9 g/dL and by 1.0 g/dL in the ITT- and in the PP populations, respectively. No statistical differences were observed between the two IUSs regarding the increase in ferritin and haemoglobin levels ($p > 0.1$).

Endometrial thickness

After one year of use, mean endometrial thickness was reduced by 7.3 mm in the Levosert® group and by 6.9 mm in the Mirena® group, among the ITT population. In the PP population, mean endometrial thickness was reduced by 7.8 mm and by 7.4 mm in the Levosert®- and the Mirena® group, respectively (Figure 6). Differences between the two treatments were not statistically significant ($p > 0.1$) (Table 2).

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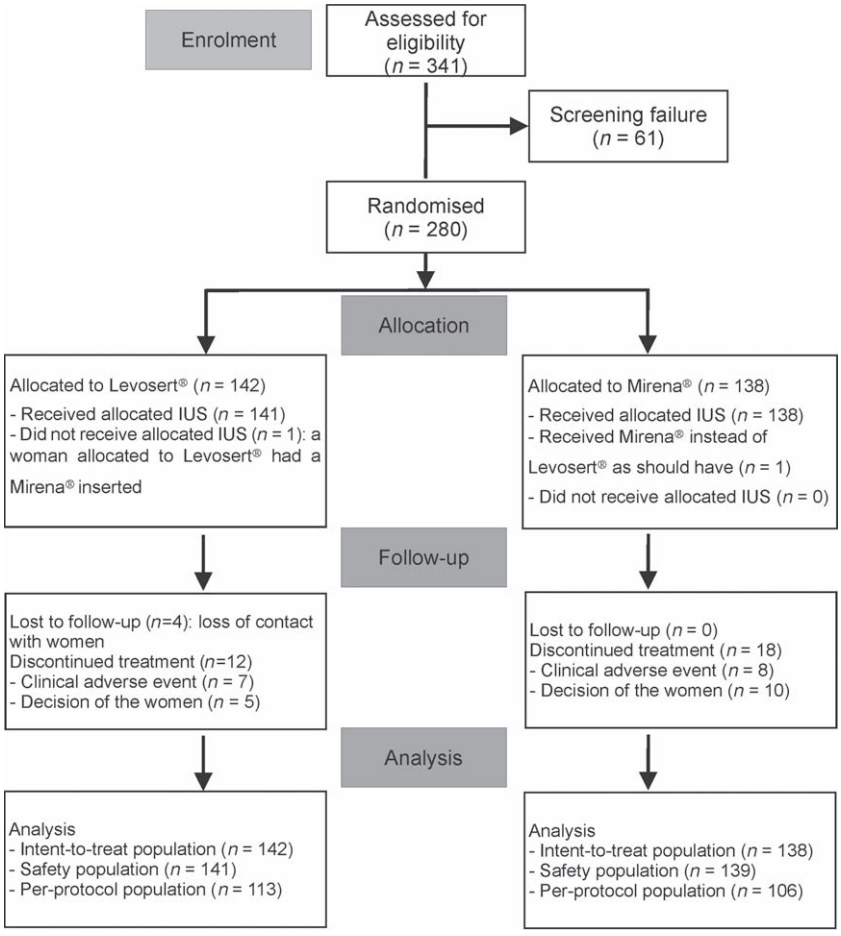

Figure 2 Randomised controlled trial profile.

Contraception

One pregnancy occurred in a woman randomised to the Levosert® group after spontaneous expulsion of the IUS in the first month after its insertion.

Adverse events

No deaths occurred during the trial. Four serious adverse events (SAEs) unrelated to the study medication were recorded in the Levosert® group (lumbar

Table 1 Baseline characteristics of the intention-to-treat population.

	Levosert® *(N = 142)*	*Mirena®* *(N = 138)*	*p-value*
Mean age, years (SD)	37.9 (± 6.2)	37.7 (± 6.1)	0.8018
Mean BMI, kg/m² (SD)	23.5 (± 3.0)	23.9 (± 3.0)	0.2485
Mean number of deliveries (SD)	1.9 (± 0.7)	1.8 (± 0.6)	0.1691
Mean MBL, mL (SD)	180.6 (± 81.9)	187.7 (± 103.4)	0.5262
Mean haemoglobin level, g/dL (SD)	12.2 (± 1.7)	12.2 (± 1.5)	0.9182
Mean ferritin level, ng/mL (SD)	21.4 (± 23.0)	22.9 (± 21.1)	0.5868
Mean endometrial thickness, mm (SD)	11.7 (± 4.4)	11.9 (± 4.6)	0.6868
Number of subjects suffering from iron deficiency anaemia	44	37	0.4412

SD, standard deviation; BMI, body mass index; MBL, menstrual blood loss.

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Table 2 Changes from baseline in menstrual blood loss (mL), ferritin (µg/L), haemoglobin (g/dL) and endometrial thickness (mm) after one year of treatment with Levosert® and Mirena® presented as least-squares mean (see Statistical analysis).

			Levosert®-Mirena® difference	
Item	*Levosert®*	*Mirena®*	*Estimate (95%CI)*	*p-value*
Menstrual blood loss (mL)				
ITT population				
Baseline, mean ± SD	180.6 ± 81.9	187.7 ± 103.4	−4.1 (−13.5 – 5.4)	0.3972
End of study, mean ± SD	35.4 ± 33.6	34.9 ± 33.5		
Change from baseline, least squares mean (95%CI)	142.3 (135.7 – 148.9)	146.4 (139.6 – 153.1)		
PP population				
Baseline, mean ± SD	181.3 ± 81.9	187.9 ± 102.1	−0.3 (-8.0 – 7.4)	0.9361
End of study, mean ± SD	33.5 ± 27.8	33.4 ± 30.2		
Change from baseline, least squares mean (95%CI)	150.9 (145.6 – 156.3)	151.2 (145.7 – 156.8)		
Ferritin level (µg/L)				
ITT population				
Baseline, mean ± SD	21.4 ± 23.0	22.9 ± 21.1	0.6 (−4.2 – 5.3)	0.8203
End of study, mean ± SD	38.5 ± 29.1	38.3 ± 26.1		
Change from baseline, least squares mean (95%CI)	16.0 (12.7 – 19.4)	15.5 (12.1 – 18.9)		
PP population				
Baseline, mean ± SD	21.8 ± 24.5	22.8 ± 20.2	−0.5 (−5.7 – 4.7)	0.8547
End of study, mean ± SD	39.8 ± 28.4	41.0 ± 25.9		
Change from baseline, least squares mean (95%CI)	17.7 (14.1 – 21.3)	18.2 (14.5 – 21.9)		
Haemoglobin level (g/dL)				
ITT population				
Baseline, mean ± SD	12.2 ± 1.7	12.2 ± 1.5	−0.2 (−2.9 – 2.4)	0.8668
End of study, mean ± SD	13.3 ± 1.2	13.2 ± 1.4		
Change from baseline, least squares mean (95%CI)	0.9 (0.7 – 1.1)	0.9 (0.86 – 1.1)		
PP population				
Baseline, mean ± SD	12.3 ± 1.6	12.4 ± 1.4	−0.4 (−3.3 – 2.5)	0.7972
End of study, mean ± SD	13.3 ± 1.2	13.4 ± 1.2		
Change from baseline, least squares mean (95%CI)	1.0 (0.8 – 1.2)	1.0 (0.8 – 1.2)		
Endometrial thickness (mm)				
ITT population				
Baseline, mean ± SD	11.7 ± 4.4	11.9 ± 4.6	0.1 (−0.3 – 1.1)	0.2282
End of study, mean ± SD	4.4 ± 2.7	4.8 ± 3.0		
Change from baseline, least squares mean (95%CI)	7.3 (6.8 – 7.8)	6.9 (6.4 – 7.4)		
PP population				
Baseline, mean ± SD	11.8 ± 4.3	12.2 ± 4.8	0.3 (−0.5 – 1.0)	0.4603
End of study, mean ± SD	4.3 ± 2.7	4.5 ± 2.7		
Change from baseline, least squares mean (95%CI)	7.8 (7.3 – 8.3)	7.4 (6.3 – 8.0)		

CI, confidence interval; ITT, intention-to-treat; SD, standard deviation; PP, per-protocol.

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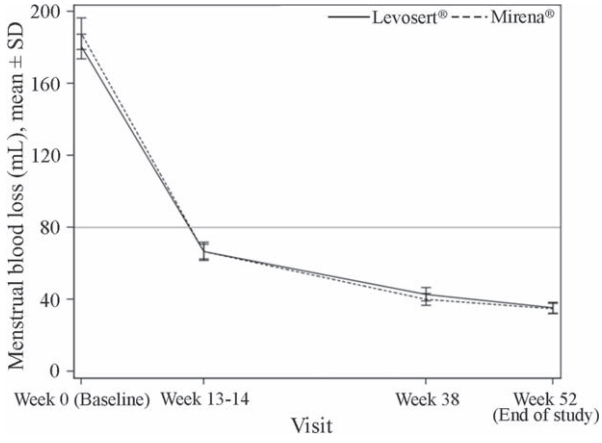

Figure 3 Decrease in menstrual blood loss (mL) over the first treatment year with Levosert® and Mirena®. ITT, intention-to-treat; SEM, standard error of the mean.

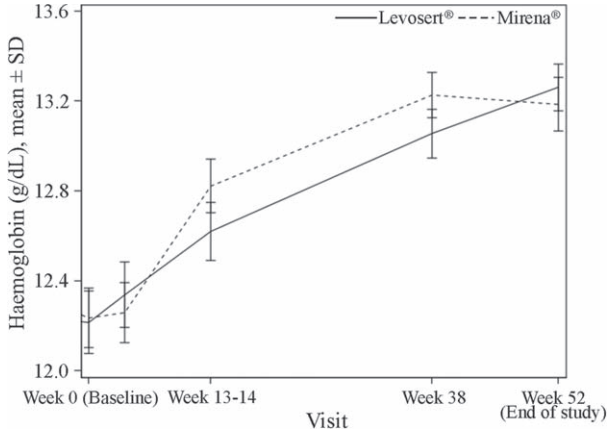

Figure 5 Increase in haemoglobin level (g/dL) over the first treatment year with Levosert® and Mirena®. ITT, intention-to-treat; SEM, standard error of the mean.

herniated disc, headache, pregnancy, and abdominal colic). One SAE was considered as possibly related to the study medication: a 49-year-old woman developed persistent bilateral translucent ovarian follicles (2.5 cm in diameter) which were found during an ultrasound performed nine months after insertion of Levosert®. Histopathological examination of the cysts removed by laparoscopy confirmed their benignity. The subject completely recovered and participated in the trial until the end. Overall, the incidence of ovarian cysts was 10% and 15.2% in the Levosert® group and in the Mirena® group, respectively.

Fifteen subjects discontinued participation in the study due to an adverse event (AE). Among them, six women in the Levosert® group and five in the Mirena® group spontaneously expelled the device. One woman in the Levosert® group left the study because of amenorrhoea and three others in the Mirena® group did so for arterial hypertension, ovarian cyst, and pelvic pain, respectively. No uterine perforation was observed in either group. Table 3 displays the treatment-related AEs reported by at least 5% of the women in each group. All those pertaining to Levosert® were anticipated as they have been described in association with the use of Mirena®. AEs were reported almost with the same frequency in both groups. The adverse event most frequently mentioned was a 'prolonged menstrual cycle'. The incidence of true amenorrhoea (defined as the

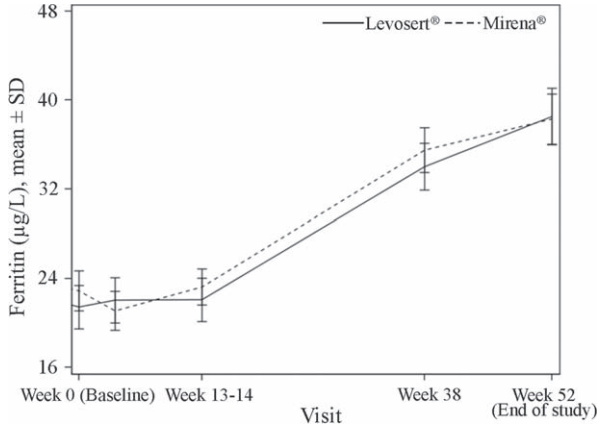

Figure 4 Increase in ferritin level (µg/L) over the first treatment year with Levosert® and Mirena®. ITT, intention-to-treat; SEM, standard error of the mean.

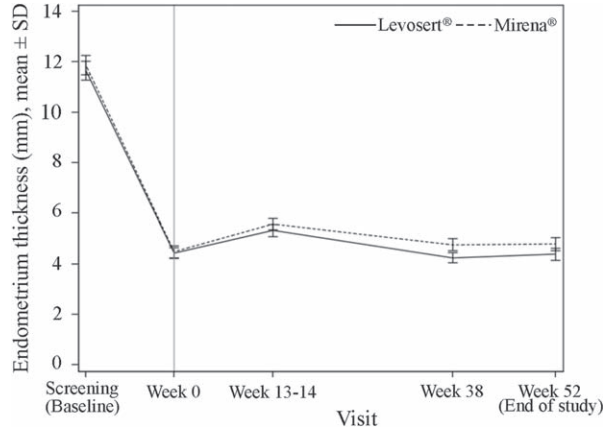

Figure 6 Decrease in endometrial thickness (mm) over the first treatment year with Levosert® and Mirena®. ITT, intention-to-treat; SEM, standard error of the mean.

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absence of menses during ≥90 days) was only half that of prolonged menstrual cycle, and was comparable in both groups. Patients may consider absence of menstrual or withdrawal bleeding as an additional benefit rather than a nuisance, depending on societal and cultural views. The incidence of spotting was high during the first three months following insertion of the IUSs but decreased dramatically thereafter. Similarly, HMB was still observed in the beginning of the study but tended to disappear after two months of treatment. Users complained of pain after insertion of the IUS with the same frequency in both Levosert® and Mirena® groups (7.1% and 6.5%, respectively).

Table 3 Drug-related adverse events occurring in at least 5% of the women of each treatment group.

Adverse events	*Levosert® (N = 141) n (%)*	*Mirena® (N = 139) n (%)*
Prolonged menstrual cycle	44 (31)	49 (35)
Spotting between menses	41 (29)	50 (36)
Amenorrhoea	21 (15)	24 (17)
Ovarian cyst	14 (10)	21 (15)
Breast tension	6 (4)	11 (8)
Heavy menstrual bleeding	11 (8)	8 (6)
Pain after IUS Insertion	10 (7)	9 (6)

IUS, intrauterine system.

DISCUSSION

Findings and interpretation

In this trial, the reference product Mirena® was compared to a new LNG-IUS called Levosert® that releases daily a similar amount of LNG. Both treatment modalities reduced MBL to the same extent (Levosert®: by 79.0% ± 18.2%; Mirena®: by 79.2% ± 19.8%). Serial TVUSs confirmed that both IUSs caused a comparable, dramatic thinning of the endometrium, as early as three months after the initiation of treatment (Figure 6), confirming the previously documented endometrial atrophy caused by locally applied LNG[20]. The important decrease in endometrial thickness between the screening period and the insertion of the IUS results from the fact that, at screening, that thickness was measured during the secretory phase of a spontaneous ovulatory cycle while, at IUS insertion, it was measured during the menstrual period.

The haemoglobin concentration and the plasma levels of ferritin increased progressively as MBL diminished. There were no statistical differences observed between the two groups.

One pregnancy occurred during the trial in a woman included in the Levosert® group, after expulsion of the device, probably during the preceding menses. Seven and eight women in the Levosert® and Mirena® groups, respectively, prematurely discontinued their partaking in the study because of adverse reactions. The incidence of drug-related adverse events was similar in both groups (Table 3) and is in line with previous studies conducted with Mirena® for contraception or HMB indications. The expulsion rates were 4.2% and 3.6% in the Levosert® and the Mirena® groups, respectively, a lower incidence than that reported in the Mirena® HMB studies. Kaunitz *et al.*, in their pivotal paper, mentioned a 4.5% expulsion rate while Xiao *et al.*, Kriplani *et al.* and Shaw *et al.*, in their limited series on Mirena®, reported even higher and – to many practitioners used to inserting intrauterine contraceptives – surprising expulsion rates of 12%, 9.5% and 6%, respectively[12,21–23]. Overall, both treatments were well tolerated. There were no differences between the two IUSs with respect to the pain experienced by the women during or after insertion.

Strengths and weaknesses of the study

This study demonstrates that both IUSs have similar safety and efficacy profiles when used for the treatment of HMB. One limitation of our trial, due to the distinct IUS aspects and insertion techniques, was its single-blind nature (i.e., the gynaecologist knew which IUS was inserted whereas the woman did not). This could have influenced the perception of the specialist regarding the efficacy and/or the safety profile of the treatments and possibly have biased the results. Therefore, an objective criterion independent of the investigator's opinion (reduction of MBL) was selected as the primary endpoint. The efficacy of Levosert® in that respect was also compared with that of Mirena® by measuring their impact on plasma ferritin and on haemoglobin. The possible subjective opinion of the investigators could not have had any bearing on the primary endpoint and other bleeding-related

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parameters. The similarity of the data pertaining to both groups supports the equivalence of the two treatment modalities and indicates that single blinding likely had no influence on the results.

Differences in results and conclusions in relation to other studies

The reduction in MBL achieved by the LNG-IUS differs greatly between studies, with results ranging from 50 to 85% after six months of treatment[24–26] and from 69 to 95% after one year[25,27–31]. These differences are probably the consequence of the heterogeneity of the underlying causes of HMB. In this study, we therefore excluded all women with structural endometrial or uterine abnormalities.

Relevance of the findings: Implications for clinicians

Recurrent HMB may result in iron deficiency and anaemia[32], classically defined by a haemoglobin level < 12.0 g/dL associated with a ferritin level < 15 ng/mL. This condition may lead to lasting fatigue, palpitations and malaise which interfere with daily activities. As observed in other LNG-IUS trials[8,32], more than 25% women allocated to both groups suffered at baseline from iron deficiency anaemia. Given the prevalence of anaemia, it is crucial to assess the changes in haemoglobin and ferritin levels when treating HMB. The favourable effects of the LNG-IUS on haemoglobin and ferritin levels were first reported in 1982 by Heikkila *et al.*[33] and they have been confirmed by many other investigators[21,27,29,30,33,34]. In this trial, the haemoglobin and ferritin levels rose steadily and had not reached a plateau after 52 weeks of treatment indicating the very progressive correction of the iron deficiency anaemia. These data suggest that iron supplementation may be beneficial in addition to the LNG-IUS. Concomitant iron supplementation was allowed during the course of the study but was taken by a very limited and similar proportion of subjects in both groups (three and one subjects in the Levosert® and the Mirena® groups, respectively).

Unanswered questions and future research

As detailed in Contraceptive Technology Update dated September 2013, the contraceptive efficacy of Levosert® is presently being assessed in a large US clinical trial conducted by Medicines 360, a San Francisco-based non-profit pharmaceutical company, with an eye to making LNG-IUS available at a low price to public sector clinics[35].

CONCLUSION

The new IUS releasing controlled amounts of LNG, Levosert®, is equally efficacious during the first year of use as the reference product Mirena® for treating HMB. Both IUSs have similar safety profiles and are commensurately well-tolerated.

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