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CLINICAL ARTICLE

A clinical study assessing the efficacy of a new variant of the levonorgestrel intrauterine system for abnormal uterine bleeding

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ABSTRACT

Objective: To evaluate the efficacy and safety of a new variant of the levonorgestrel–intrauterine system (LNG-IUS)—Emily—for the treatment of abnormal uterine bleeding (AUB). *Methods:* A prospective, multicenter, single-arm, phase 4 study was conducted at six centers in India between July 2012 and August 2013. Eligible women were aged 30–50 years, had completed their family, had AUB, and a pictorial bleeding assessment chart (PBAC) score of at least 100. After screening (visit 1) and insertion of the device (visit 2), participants were followed up at 1 week, 1 month, 3 months, and 6 months. The primary outcomes were menstrual blood loss (assessed by PBAC) and quality of life (assessed by the EQ-5D-3 L questionnaire). *Results:* Among 63 participants, 45 (71%) completed the study. Mean PBAC score decreased from 238.0 ± 128.7 at screening to 13.1 ± 19.2 at 6 months ($P < 0.001$). EQ-5D-3 L score increased from 79.0 ± 14.1 at visit 2 to 86.3 ± 9.0 at 6 months ($P = 0.003$). No serious adverse events related to the device were reported. *Conclusion:* Among women with AUB, use of the Emily LNG-IUS significantly reduces menstrual bleeding and improves quality of life.
Clinical Trials Registry of India: CTRI/2012/07/002843

1. Introduction

Abnormal uterine bleeding (AUB) is one of the most common bleeding symptoms in many premenopausal women [1]. AUB is reportedly experienced by approximately 30% of women of reproductive age and accounts for nearly 60% of consultations for menstrual disorders [2].

Drug therapy for AUB includes oral contraceptives, progestins, tranexamic acid, and nonsteroidal anti-inflammatory drugs. If oral drug therapy becomes ineffective, surgical procedures for AUB can be considered, such as hysterectomy, endometrial resection, and laser ablation. Additionally, repeat surgeries are relatively common with as many as 30% of the women undergoing endometrial resection or laser ablation opting for hysterectomy [2,3].

The levonorgestrel intrauterine system (LNG-IUS) is considered to be the most effective medical treatment for AUB [4]. The LNG-IUS was introduced for contraception in 1990 and currently there are an estimated 4 million LNG-IUS users worldwide [5]. The US Food and Drug Authority has approved LNG-IUS both for use as a contraceptive and for the treatment of menorrhagia [6].

In India, use of LNG-IUS for the treatment of AUB is relatively low owing to various reasons, such as poor availability, few competing brands, and high cost [7,8]. Therefore, many women with AUB who become refractory to drug therapy are forced to opt for hysterectomy. In addition, the prevalence of anemia among Indian women could be as high as 52%, and the concomitant presence of anemia might further worsen the health of women with AUB [5]. Therefore, LNG-IUS would be likely to improve the health of these women, which prompted HLL Lifecare Ltd and Sree Chitra Tirunal Institute of Medical Science and Technology to develop an affordable new variant of LNG-IUS—Emily—for the treatment of AUB. The device was approved on October 11, 2011, by the drugs controller and licensing authority, and was launched on the Indian market on October 18, 2012. The aim of the present clinical study was to assess the efficacy and safety of Emily for the treatment of women with AUB.

2. Materials and methods

The present prospective, multicenter, single-arm, phase 4 study of the Emily LNG-IUS was conducted among women recruited at six different centers in four cities in India (Mumbai, Delhi, Hyderabad, and Bangalore) between July 22, 2012, and August 3, 2013. Eligible women were aged 30–50 years; had completed their family (as ascertained by direct interaction with the women); had a non-

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demonstrable pathologic cause of AUB as defined by the International Federation of Gynecology and Obstetrics (FIGO) PALM-COEIN classification [9] (e.g. coagulopathy, ovulatory dysfunction, or endometrial dysfunction) and evidenced by heavy menstrual bleeding for a minimum of the past three cycles; and a baseline pictorial bleeding assessment chart (PBAC) score of 100 or more.

The exclusion criteria were a confirmed or suspected pregnancy; delivery, or spontaneous or induced abortion in the previous 3 months; intermenstrual bleeding; postmenopausal bleeding (bleeding occurring more than 1 year after the last menstrual period); demonstrable pathologic causes of AUB, such as endometrial polyp and myoma uteri, pelvic inflammatory disease, untreated acute cervicitis or vaginitis, or congenital abnormality of the uterus; an abnormal cervical smear report; diabetes mellitus or uncontrolled hypertension; a history of incapacitating migraine, cerebrovascular disease, coronary artery disease, thrombophlebitis, or thromboembolism; known or suspected tumors of the liver, kidney, ovary, uterus, cervix, or breast; use of prohibited medication (hepatotoxic drugs or herbal products) in the past month; immunosuppressive treatment; known hypersensitivity to micronized progesterone, silicone rubber, or any component of the investigational product; or levels of thyroid-stimulating hormone (TSH) of less than 0.4 IU/mL or more than 7 IU/mL, or abnormal levels of triiodothyronine (T3; <3.47 nmol/L or >6.94 nmol/L) or thyroxine (T4; <124.15 nmol/L or >309.01 nmol/L).

The study protocol was reviewed and approved by the institutional review board or institutional ethics committee at each of the study sites. All participants provided written informed consent.

The study was conducted in two phases: screening (visit 1, 1–7 days before insertion) followed by 6 months of treatment visits. At the screening visit, a cervical smear was done for women who had not had one in the previous 9 months. Additionally, laboratory assessments (e.g. complete blood count, liver function test, and a test for TSH) and pelvic ultrasonography to rule out pelvic pathology were performed. A urine pregnancy test was also performed during the screening phase and 6 months after insertion.

The Emily device was inserted on visit 2, which took place during the first 7 days of the participant's menstrual cycle. During the insertion procedure, feedback was gathered from the subjects regarding any discomfort during the insertion of the device. The Emily device consists of three major components: 1) an M-shaped flexible plastic arm; 2) a drug reservoir, which is a room-temperature vulcanizing, siloxane-based elastomer impregnated with levonorgestrel; and 3) a regulating membrane, which is a reinforced siloxane-based elastomer. Levonorgestrel is incorporated into the elastomer by shear mixing for 30 minutes using a Planetary Centrifugal mixer, and the elastomer is formed into the desired shape with appropriate molds. The regulating membrane is fabricated by using a siloxane-based elastomer incorporated with reinforcing filler. The length of the horizontal arm is 19.5 mm, the height of the vertical stem is 36 mm, and the core length is 23.5 mm (Fig. 1).

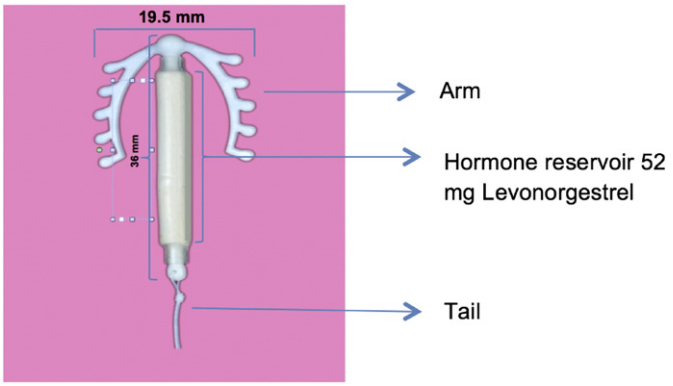

Fig. 1. Dimensions of Emily, a new variant of the levonorgestrel intrauterine system.

After insertion, participants were followed up at 7 ± 1 days (visit 3), 30 ± 4 days (visit 4), 90 ± 4 days (visit 5), and 180 ± 4 days (visit 6).

The primary outcomes assessed were menstrual blood loss as measured with PBAC, and quality of life as measured by the EQ-5D-3 L questionnaire at visits 4 and 6. A speculum examination was performed at visits 4–6 months to ensure proper placement of the LNG-IUS. Menstrual blood loss at each cycle was assessed by PBAC, and the participants were trained to accurately record the PBAC score in a diary during menstruation. Participants with a PBAC score greater than or equal to 100 were deemed to have a menstrual blood loss of 80 mL and therefore AUB [10]. The EQ-5D-3 L questionnaire measures quality of life in terms of mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. Hemoglobin levels were measured via the cyanmethemoglobin method at visits 4 and 6. Standardized sanitary pads (Stayfree secure regular use, Johnson & Johnson, Mumbai, India) were issued upon completion of the PBAC questionnaire.

The treatment was deemed to have failed if there was confirmed expulsion of the LNG-IUS, the participant withdrew from the study, or alternative therapy was initiated. Treatments were otherwise deemed not to have failed, but with varying levels of participant satisfaction.

The in vitro release of levonorgestrel from Emily was also compared with that of an LNG-IUS device already on the market (Mirena, Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA). The fabricated prototypes of Emily, along with the comparator LNG-IUS, were transferred to 10 mL of simulated uterine fluid in 30-mL glass vials in a laminar flow cabinet in a sterile environment. The devices were maintained on an incubator shaker at 37 °C at 100 rpm to mimic a physiological environment to measure the in vitro release of levonorgestrel. At weekly intervals, the supernatant was removed and the devices were transferred to 10 mL of fresh simulated uterine fluid to continue monitoring the drug elution profile. The supernatants were analyzed by high-performance liquid chromatography to determine the release of drug over time. Because the concentration of levonorgestrel reached in plasma and endometrial tissue is as low as 150–200 pg/mL and 808 ± 511 ng/g, respectively [6], it was not feasible to compare the in vivo concentrations of levonorgestrel between Emily and other devices.

A sample size of 56 was deemed sufficient to prove that Emily is not materially different from Mirena, at 95% confidence and 80% power, with regard to a reduction in PBAC by 91% (the higher of two published values after 6 months of Mirena use) and an assumed worst value of 85% for Emily with a non-inferiority limit (delta) of 10% between the proportions. Assuming a 10% drop-out, the necessary sample size became 62. Even though the comparison available was with historical values for Mirena, the 100(1–2α)% confidence interval approach was used (where $\alpha = 0.05$).

Statistical analysis was performed with SPSS version 17 (SPSS Inc, Chicago, IL, USA). Women who completed 6 months of the study were included in analyses. Continuous data are reported as the mean ± SD and median (range). Proportions of various intermediate outcomes are given as percentages. The mean and median of the total PBAC score were calculated at visits 5 and 6, in addition to the proportion of women with amenorrhea. The average reduction in total PBAC score was calculated as a percentage. Paired *t* tests were used to compare values between baseline and visit 5, and baseline and visit 6 after assigning a value of 0 to the participants with amenorrhea. EQ-5D-3 L values for visits 2 and 6 were also compared. $P < 0.05$ was taken as statistically significant.

3. Results

Among 86 patients who were assessed for eligibility, 63 were enrolled (Fig. 2). Among the 23 who were excluded, six had raised serum glutamic oxaloacetic transaminase or serum glutamic pyruvic transaminase levels, five had hypothyroidism, two had a smear test showing inflammation with mild dysplasia, and 10 had an abnormal

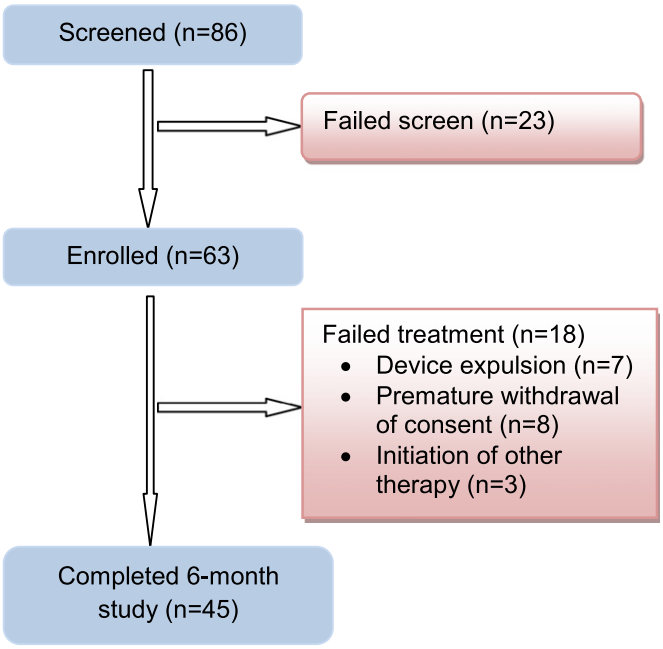

Fig. 2. Flow of participants through the study.

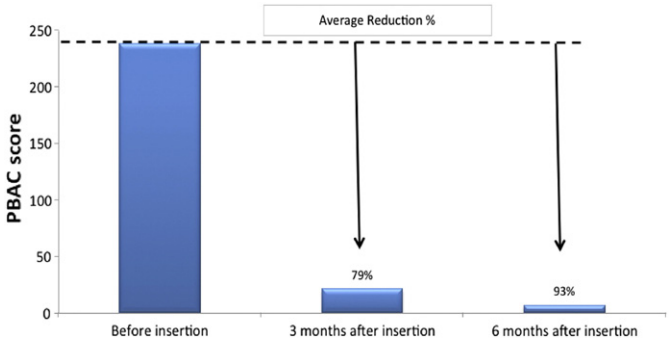

Fig. 3. PBAC score. Abbreviation: PBAC, pictorial bleeding assessment chart.

ultrasonography report showing fibroids, endometritis, or complex hyperplasia with atypia.

The baseline characteristics of the 63 women enrolled in the study are given in Table 1. All participants were of Asian ethnic origin. During the study, 18 (29%) women experienced treatment failure (Fig. 2).

Among the 45 patients who completed 6 months, PBAC score had decreased significantly between baseline and 3 and 6 months ($P < 0.001$ for both) (Table 2, Fig. 3). Menorrhagia was the most common adverse effect, having been reported by 10 (16%) of the 63 patients enrolled. Four of these women had the Emily LNG-IUS removed. Amenorrhea was reported by 15 (33%) of the 45 women included in analyses at 3 months, and 21 (47%) at 6 months. No serious adverse events related to the device were reported. Postinsertion feedback gathered regarding any discomfort during the insertion revealed that the device is not associated with any significant discomfort. In terms of quality of life, mean EQ-5D-3 L score improved between visit 2 and visit 6 ($P = 0.003$) (Table 3). Mean hemoglobin levels increased from 114.8 ± 15.8 g/L at visit 1 to 123.6 ± 12.6 g/L at visit 6.

The in vitro release profile of Emily is shown in Fig. 4. The average release of levonorgestrel per day from an LNG-IUS device is reported to be 20 μg [6]. Therefore, the in vitro release profile is similar to that of other LNG-IUS devices.

4. Discussion

The present study has shown that mean PBAC score among women with AUB decreases substantially after insertion of the Emily LNG-IUS device. Only approximately 30% of participants experienced treatment failure. There was a slight improvement in quality of life at 6 months after Emily insertion in terms of mobility, self-care, usual activities, pain, anxiety, and depression. Insertion of the device was not associated with any notable discomfort.

One of the primary outcomes of the present study was the efficacy of the Emily LNG-IUS, as assessed by a reduction in menstrual blood loss using PBAC. When used judiciously, the PBAC scoring system has been shown to accurately quantify menstrual blood loss [11]. In the present study, the participants were trained after their enrollment to follow the PBAC scoring system.

In the present study, the average percentage reduction in the mean PBAC score at 3 and 6 months (79% and 93%, respectively) was similar to existing data for the LNG-IUS, which have been reported as 86% and 91% at 3 and 6 months, respectively [12]. In another study [13], the percentage reduction in menstrual blood loss at 3 and 6 months was found to be 82% and 88%, respectively. The 100(1–2α)% confidence limits for the difference between the individual values of percentage reduction in PBAC after Emily use in the present study and the mean reduction of 91% in PBAC after 6 months of Mirena use were derived. They were calculated to be –0.6% and 4.8%, which were well within the range of ± 10%, thus vindicating the non-inferiority stance in sample size calculation.

A point of concern is the high rate of device expulsion in the present study (11%; n = 7). A previous report [14] suggested that the expulsion rate for LNG-IUS is approximately 5%. The expulsion rate among the 45 women who completed the present study is continuing to be monitored in a post-marketing surveillance study, and stood at 4% (1 of 45 women)

Table 1
Baseline characteristics (n = 63).

Characteristic	Mean ± SD	Median (range)
Age, y	39.0 ± 6.0	39 (28–49)
Height, cm	155.5 ± 6.6	155 (135–173)
Weight, kg	65.9 ± 13.7	64 (38–96)
Frequency of menstruation in past 3 cycles, d[a]	28.9 ± 2.7	29 (25–36)
PBAC score	234.0 ± 121.6	201 (104–900)

Abbreviation: PBAC, pictorial bleeding assessment score.
[a] If regular.

Table 2
Menstrual status of the study women at 3 and 6 months (n = 45).

Time	Amenorrhea[a]	Total PBAC score	
		Mean ± SD	Median (range)
Baseline	0	238.0 ± 128.7	208 (112–900)
Visit 4	15 (33)	46.2 ± 73.6[b]	10 (0–382)
Visit 6	21 (47)	13.1 ± 19.2[b]	2 (0–63)

Abbreviation: PBAC, pictorial bleeding assessment chart.
[a] Values are given as number (percentage).
[b] Significantly different from baseline ($P < 0.001$).

Table 3
Quality of life score (n = 45).

Visit	EQ-5D-3 L questionnaire score	
	Mean ± SD	Median (range)
2	79.0 ± 14.1	81 (50–100)
6	86.3 ± 9.0[a]	90 (60–100)

[a] Significantly different from visit 2 ($P = 0.003$).

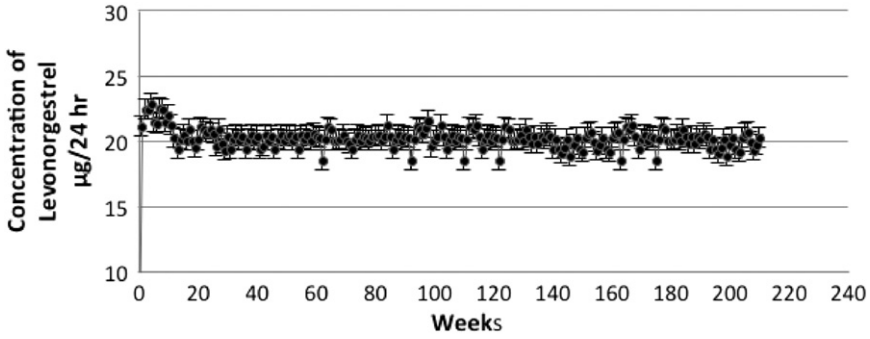

Fig. 4. In vitro release profile of the Emily levonorgestrel intrauterine system.

at the time of publication; a clearer picture will emerge as the study progresses. One reason for the high rate of expulsion in the present study could be that the physicians had been using Emily for the first time.

Although not a primary objective of the present study, mean hemoglobin levels had improved slightly 6 months after Emily insertion. Because anemia can worsen the health of women with AUB [5], it is expected that Emily will also improve the health condition of these women.

A larger sample size would have provided more insight into the use of Emily among patients, especially in relation to events such as expulsions and safety. This aspect will be considered in the Emily post-marketing surveillance study.

In conclusion, the Emily LNG-IUS could be used to reduce menstrual bleeding and improve the quality of life of women with AUB. Before Emily was developed, the cost of existing LNG-IUS devices was approximately US$135, making them unaffordable for most women in India. Emily costs approximately US$41, bringing the device within the reach of most patients. Another advantage is its innovative M-shaped frame, which enables it to be placed in the uterus without an inserter device—an important factor in reducing cost.

Acknowledgments

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Conflict of interest

The authors have no conflicts of interest.

References

[1] Monteiro I, Bahamondes L, Diaz J, Perrotti M, Petta C. Therapeutic use of levonorgestrel-releasing intrauterine system in women with menorrhagia: a pilot study(1). Contraception 2002;65(5):325–8.

[2] Stewart A, Cummins C, Gold L, Jordan R, Phillips W. The effectiveness of the Mirena coil (levonorgestrel-releasing intrauterine system) in menorrhagia: a West Midlands Development and Evaluation Service report. http://www.birmingham.ac.uk/Documents/college-mds/haps/projects/WMHTAC/REPreports/1999/menorrhagia.pdf. Published December 1999. Accessed January 21, 2015.

[3] Wheeler II TL, Murphy M, Rogers RG, Gala R, Washington B, Bradley L, et al. Clinical practice guideline for abnormal uterine bleeding: hysterectomy versus alternative therapy. J Minim Invasive Gynecol 2012;19(1):81–8.

[4] Nelson AL. Levonorgestrel intrauterine system: a first-line medical treatment for heavy menstrual bleeding. Womens Health (Lond Engl) 2010;6(3):347–56.

[5] Hurskainen R, Teperi J, Rissanen P, Aalto A, Grenman S, Kivelä A, et al. Clinical outcomes and costs with the levonorgestrel-releasing intrauterine system or hysterectomy for treatment of menorrhagia: randomized trial 5-year follow up. JAMA 2004;291(12):1456–63.

[6] Willett G. Clinical review: Mirena (levonorgestrel-releasing intrauterine system). http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM245685.pdf. Published 2009. Accessed January 20, 2015.

[7] Reproductive Health Supplies Coalition. Product brief: caucus on new and underused reproductive health technologies. http://www.path.org/publications/files/RHSC_all_br.pdf. Published March 2012. Accessed December 5, 2013.

[8] Magon N, Chauhan M, Goel P, Malik S, Kapur K, Kriplani A, et al. Levonorgestrel intrauterine system: current role in management of heavy menstrual bleeding. J Midlife Health 2013;4(1):8–15.

[9] Munro MG, Critchley HO, Broder MS, Fraser IS, FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynecol Obstet 2011;113(1):3–13.

[10] Lee JY, Hahn PM, Van Dijk JP, Reid RL. Treatment of menorrhagia with tranexamic Acid. J Soc Obstet Gynaecol Can 2000;22(10):794–8.

[11] Zakherah MS, Sayed GH, El-Nashar SA, Shaahban MM. Pictorial blood loss assessment chart in the evaluation of heavy menstrual bleeding: diagnostic accuracy compared to alkaline hematin. Gynecol Obstet Invest 2011;71(4):281–4.

[12] Andersson JK, Rybo G. Levonorgestrel-releasing intrauterine device in the treatment of menorrhagia. Br J Obstet Gynaecol 1990;97(8):690–4.

[13] Milsom I, Andersson K, Andersch B, Rybo G. A comparison of flurbiprofen, tranexamic acid, and a levonorgestrel-releasing intrauterine contraceptive device in the treatment of idiopathic menorrhagia. Am J Obstet Gynecol 1991;164(3):879–83.

[14] Busfield RA, Farquhar CM, Sowter MC, Lethaby A, Sprecher M, Yu Y, et al. A randomised trial comparing the levonorgestrel intrauterine system and thermal balloon ablation for heavy menstrual bleeding. BJOG 2006;113(3):257–63.