A Levonorgestrel-Releasing Intrauterine System for the Treatment of Idiopathic Menorrhagia

MOHAMED ABD ELZAHER, M.D. 1,2; ASHRAF MOAWAD, M.D. 1,3 and HANAA ABU-RIA, M.D. 1,4

The Departments of Obstetrics & Gynecology, Al-Azhar University, Cairo, Egypt 1; King Khalid University Hospital, KSA 2; Enjab Hospital for Infertility, UAE 3 and Gulf Medical College & Research Centre, UAE 4

Abstract

Objective: To determine whether the levonorgestrel-releasing intrauterine system can safely reduce menstrual blood loss and improve quality of life in patients with idiopathic menorrhagia.

Study Design: Prospective Multicentre study.

Setting: Obstetrics and Gynecology Departments (King Khalid University Hospital-KSA, Enjab Hospital for infertility-UAE and Gulf Medical College and Research Centre-UAE).

Patient(s): Forty patients with MBL over 80ml.

Intervention(s): Insertion of the LNG-IUS on cycle days 5-7 and follow-up at 6-month intervals for 3 years.

Main Outcome Measure(s): Measurement of MBL, serum ferritin, and hemoglobin for evaluation of efficacy of treatment.

Result(s): A significant reduction of MBL to 36.3mL (77.9% decrease), 30.5mL (81.7% decrease), 7.9mL (95.3% decrease), and 23.5mL (85.7% decrease) at 6, 12, 24, and 36 months, respectively. After 6 months, one-fourth of the patients experienced amenorrhea, and one-third, spotting. Hemoglobin increased significantly from 12.2g/dl pre insertion to 13.4g/dl after 36 months, while serum ferritin levels increased significantly from 21.9ng/mL before insertion to 92.8ng/mL after 36 months.

Conclusion(s): The LNG IUS was associated with a profound reduction in menstrual blood loss and the increase in hemoglobin and serum ferritin levels in the treatment of idiopathic menorrhagia.

Key Words: Levonorgestrel-releasing intrauterine system – Idiopathic menorrhagia – Menstrual blood loss – Serum ferritin – Hemoglobin.

Introduction

THE levonorgestrel-releasing intrauterine system (LNG-IUS) (Mirena, Schering) was originally designed as a contraceptive method registered in Europe, Latin America, U.S., and Canada [1,2]. Intrauterine devices (IUDs) provide highly effective, long-term, safe, reversible contraception, and are the most widely used reversible contraceptive method worldwide. The levonorgestrel-releasing intrauterine system (LNG-IUS) is a T-shaped IUD with a steroid reservoir containing 52mg of levonorgestrel that is released at an initial rate of 20µg+ daily. It is highly effective, with a typical-use first year pregnancy rate of 0.1%—similar to surgical tubal occlusion. It is approved for 5 years of contraceptive use, and there is evidence that it can be effective for up to 7 years of continuous use [3].

After removal, there is rapid return to fertility, with 1-year life-table pregnancy rates of 89 per 100 for women less than 30 years of age [4]. Most users experience a dramatic reduction in menstrual bleeding, and about 15% to 20% of women become amenorrheic 1 year after insertion. The device’s strong local effects on the endometrium benefit women with various benign gynecological conditions such as menorrhagia [5,6] dysmenorrhea [7], leiomyomata [8], adenomyosis [7], and endometriosis [9].

There is also evidence to support its role in endometrial protection during postmenopausal estrogen replacement therapy, and in the treatment of endometrial hyperplasia [10]. The active ingredient, levonorgestrel (LNG), is dispersed in a silicone (polydimethylsiloxane) reservoir on the stem. This reservoir contains 52mg of LNG, and is covered by a polydimethylsiloxane membrane.

Abbreviations:

MBL : Menstrual blood loss.
Hb : Haemoglobin.
LNG-IUS : Levonorgestrel releasing-intrauterine system.
PBAC : Pictorial blood assessment chart.
Pts : Patients.
which allows for a controlled release of the hormone over time. The initial release rate of approximately 20µg per day occurs after insertion, and gradually decreases to approximately 10µg per day after 5 years of use [11].

Idiopathic menorrhagia is one of the common gynecological diseases seen in the outpatient clinics of many general hospitals and gynecology clinics. Women suffering from heavy monthly bleeding are often anemic and in ill health, both physically and mentally. Each month before the expected days of menstruation they are under mental stress at home and at work.

Patients with menorrhagia often resort to treatment with traditional herbal medicine first and then use steroids, such as nore-thisterone, megestrol acetate, or even testosterone propionate injectables during heavy bleeding. When medical treatment fails, the last resort is surgical intervention. Curettage is often used as an emergency measure to treat heavy bleeding [12,13,14]. Endometrial ablation is not very popular and is only performed in a few Hospitals [5].

Only when all methods fail after many years of treatment and the patient is very ill does the patient resort to hysterectomy. The fact that use of the LNG-IUS can effectively treat menorrhagia brings hope to these women [15]. The profound reduction in bleeding associated with LNG-IUS use not surprisingly results in sustained increases in hemoglobin, hematocrit, and serum ferritin. Long-term follow-up studies of LNG-IUS in healthy women have demonstrated favorable sustained increased from baseline in hemoglobin concentrations with a mean increase of 1.6g/dL after 5 years of use and 1.44g/dL after 7 years of use [15,16].

The aim of this study was to determine whether the levonorgestrel-releasing intrauterine system can safely reduce menstrual blood loss and improve quality of life in patients with idiopathic menorrhagia.

Material and Methods

A Prospective multicentre study was conducted between December 2007 to June 2011, at the Departments of Obstetrics and Gynecology, King Khalid University Hospital (KKUH), Enjab Hospital for infertility and Gulf Medical College and Research Centre. Forty women reported recurrent menorrhagia of at least 18 months duration. All women to be included in the study were screened for their clinical suitability for IUD insertion and followed-up for 36 months duration. Each woman underwent pelvic examination, transvaginal ultrasound; Pipelle endometrial biopsy and Papanicolaou smear in the 2 months before entry into the study to evaluate the uterine status. All women voluntarily signed an informed consent to the study.

The inclusion criteria include: Age of 30-50 years, and absence of pregnancy or breastfeeding. Normal Sized or slightly enlarged uterus, and no current or history of pelvic Inflammatory disease within the last 3 months. Also no current or history of sexually transmitted diseases within the last 3 months, and absence of distortion of the uterine cavity.

Patients with the following were excluded: Congenital valvular heart disease or congenital malformation of the vagina, cervix or uterus. Known or suspected uterine or cervical malignancy, or History of pelvic inflammatory disease (PID). Also a history of postpartum endometrities or history of infected abortion.

Demographic and baseline clinical data, including, menstrual blood loss, blood hemoglobin, and serum ferritin concentrations, were obtained before the LNG IUS insertion. The LNG IUS releasing levonorgestrel 20g/day (Mirena; Leiras OY, Turku, Finland) was inserted within 5-7 days of the menstrual cycle. Participants were followed-up four times thereafter (at the end of 6,12,24,36 months) to repeat these measurements and compare them with the baseline values.

Menstrual blood loss was estimated using a pictorial blood loss assessment chart devised by Higham et al. [17]. To minimize inter observer variation, we provided all patients the same sanitary protection product in all three setting of study. The patients completed the charts for one menstrual cycle prior to the LNG IUS insertion, and for the entire 6,12,24,36 months afterward. We evaluated the completed charts according to the scoring system. The pictorial blood assessment chart score 100 is equivalent to blood loss of 80mL, which defines menorrhagia [3]. The following analyses are based on samples taken at different time intervals. In some cases, because of very scanty spotting, MBL was not measurable, and in cases of amenorrhea no samples were collected. Therefore, the samples analyzed were fewer than the number of patients at each follow-up visit. Serum ferritin and hemoglobin levels were measured at 3,6,12,24 and 36 months. Patients were asked not to use other hormonal contraceptive methods or other drug treatment (e.g., iron) for bleeding or anemia until the end of the study.
At the end of study after 36 months, Pipelle endometrial biopsy was repeated to evaluate the endometrial status. These specimens were fixed and haematoxylin and eosin stained sections were produced in a standard manner, and were assessed by a consultant histopathologist of the hospital. At the conclusion of study, satisfaction was assessed on a scale of four, from satisfied to extremely satisfied.

Statistical analysis was performed using SPSS version 15 software. Changes in hemoglobin and serum ferritin levels before and after insertion of the LNG-IUS were analyzed by the paired $t$-test. In analyzing MBL data, Wilcoxon’s signed rank test (nonparametric) was used. A Probability level ($p$) of less than 0.05 was considered significant.

**Results**

A total of 40 parous women, with the mean age at admission was 35 years (SD 4.4; range, 30–50 years). The mean weight was 59.9kg (SD 8.1; range 40–80kg). The mean height was 162cm (SD 5.5; range 151–170cm). The mean body mass index (BMI) was 21.7 (SD 1.9; range 14.3–27.6). Insertion of the LNG IUS was uneventful, and was performed in all cases without anesthesia and without particular patient discomfort. No changes occurred during the study period in blood pressure. We found no abnormalities in the Papanicolaou smears. Complaints after LNG-IUS insertion were rare except for some abdominal pain (5 Pts), backache (2 Pts), headache (2 Pts), breast tenderness (2 Pts), acne (2 Pts), dysmenorrhea (2 Pts), weight gain over 5kg (6 Pts), nausea (1 Pt), and fatigue (1 Pt).

In this study we used an (LNG-IUS) that contains 52mg of levonorgestrel which is released at a rate of 20 $\mu$g daily for 5 years. We have shown that epithelial atrophy and stromal decidualization are the most typical morphological characteristics in the endometrium during the use of LNG-IUS. Menstrual blood loss is significantly decreased, and many women treated with LNG-IUS have no menstrual bleeding one year after the insertion. At the beginning of the study period, there was simple hyperplasia in 28 patients, irregular proliferative endometrium in 10 patients, and secretory endometrium in 2 patients.

*There were two complete expulsions:* One on the second day after insertion because of heavy bleeding, the second during the first month. One partial expulsions were observed during pelvic examination; the lower end of the vertical stem of the LNG-IUS protruded from the external cervical os at the 6month checkup. Two women were lost to follow-up: One at the third month and another at 16 months.

After insertion of the LNG-IUS, MBL became markedly reduced. There were many cycles where MBL was so scanty that it was not measurable, and some patients were amenorrheic. After 6 months, about one-fourth of the patients experienced amenorrhea and one-third, scanty spotting (Table 1). When compared with the average MBL before insertion (166.9mL), MBLs at 6, 12, 24 and 36 months were, 36.3, 30.5, 7.9 and 23.5mL, representing reductions of 77.9%, 81.7%, 95.3% & 85.7%, respectively. On average, the reduction of MBL was 85.2%.

| Table (1): Menstrual blood loss (MBL) before and after insertion of the levonorgestrel-releasing system. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| **Pre insertion**               | **Post insertion** |
| **No. of patients**             | 40              | 36              | 36              | 36              |
| **Measurable sample (No.)**     | 40              | 18              | 15              | 13              |
| **Mean (ml) ±SD**               | 166.9±66.6      | 36.3±31.2       | 30.5±38.8       | 7.9±4.3         |
| **Minimum**                     | 81              | 1.8             | 0.5             | 0               |
| **Maximum**                     | 290             | 138             | 167.5           | 13.5            |
| **p-value**                     | 0.0001          | 0.0001          | 0.0001          | 0.0001          |
| **Amenorrhea**                  | 8               | 9               | 14              | 5               |
| **Spotting**                    | 10              | 12              | 8               | 20              |
| **% of MBL reduction**          | 77.9%           | 81.7%           | 95.3%           | 85.7%           |

*Note:* In analyzing the MBL data, a nonparametric Wilcoxon signed rank test was used. In this analysis and for patients with amenorrhea or spotting, Values 0 and 0.5 were used, respectively. The $p$-values at each segment month are values for the comparison with the pre insertion data.
Along with the reduction of MBL, there were also significant increases of hemoglobin and serum ferritin. Hemoglobin increased from 12.2g/dl pre insertion to 13.4g/dl after 36 months; serum ferritin increased from 21.9ng/mL before insertion to 92.8ng/mL at 36 months. The differences were highly significant (Tables 2,3).

At the end of the study, Pipelle endometrial biopsy showed pronounced progesterone influence with decidua-like stroma in 23 samples, desquamated endometrium in 8 samples, and no endometrium in four. Proliferation or atypia was not found in any of the specimens. The mean endometrial thickness was greater than 5mm in women at the initial of the study. At the final screening there was a significant decrease in mean endometrial thickness less than 3mm which demonstrated an extremely thin endometrium 36 months after IUD insertion during the follow-up of our patients.

Majority of patients were extremely satisfied or satisfied and would recommend the treatment to a friend. Four (11.4%) unsatisfied patients were still more than willing to continue LNG-IUS. One had backache and three had weight gain over 5kg and with levonorgestrel.

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<th>Table (2): Hemoglobin (g/dl) before and after levonorgestrel.</th>
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Note: The paired t-test was used for comparing hemoglobin data at each segment month with the pre insertion value. The increase of hemoglobin was very significant after 6 months of treatment.

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<th>Table (3): Serum Ferritin (ng/mL) before and after levonorgestrel-releasing system insertion.</th>
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Note: The paired t-test was used for comparing serum ferritin data at each segment month with the pre insertion value. The increase of serum ferritin was very significant after 6 months of treatment.

Discussion

Menorrhagia is defined as regular, prolonged and excessive menstrual bleeding of more than 80ml from a secretory endometrium. When menstrual blood loss exceeds 80ml, the incidence of anemia increased significantly. Iron deficiency with depletion of iron stores and or anemia predisposes the women to ill health and disease [19].

The LNG-IUS was originally designed for contraceptive use more than 25 years ago. The purpose was to improve the contraceptive efficacy over that of inert intrauterine devices and to reduce side effects. Extensive studies following the introduction of the LNG-IUS revealed that its main mechanism of action differs from that of inert IUDs. The LNG-IUS is a hormonal contraceptive, but its action is local to the uterine cavity. Levonorgestrel is a 19-nortestosterone derivative which is much more potent than natural progesterone and has major effects on the stromal parts of the endometrium. Many women using the LNG-IUS have ovulatory cycles although they may have menstrual irregularities during the first few months of use [20].

The therapeutic effect of the LNG-IUS in the treatment of menorrhagia is very well illustrated in different studies by Xiao et al. [6], Kaunitz et al. [13] and Shabaan et al. [14] The levonorgestrel
intrauterine system reduces up to 86 percent of menstrual blood loss after three months in women with idiopathic menorrhagia and up to 97 percent after 12 months. At 12 months after insertion of the system, reported rates of amenorrhea vary from 20 to 80 percent. In the present study, we report the follow-up of 40 patients for 3 years, which is a long follow-up, for menstrual pattern after LNG-IUS insertion. This implies that the LNG-IUS is very well accepted by our patients. More than one-third of the women who had amenorrhea or very scanty bleeding found the LNG-IUS very satisfactory. They had previously been suffering from the bleeding both physically and mentally, with no effective treatment for a long time. They were happy to have amenorrhea, knowing that it was not pathological and was reversible.

The effectiveness of the LNG-IUS to treat menorrhagia may be caused by two actions. First, it causes strong decidualization and subsequent marked atrophy of the endometrium [22]. The LNG-IUS also affects the vascular system in the endometrium. The changes include thickening of the arterial walls and suppression of the spiral arteries and capillary thrombosis. This probably accounts for the marked reduction in menstrual flow. Secondly, there is also direct action of the hormone on endometrial tissues [20]. The LNG-IUS has been shown to cause down regulation of oestrogen receptors (ER) in both glandular and stromal endometrial tissues. This was evident at one month post insertion and persisted for up to 12 months after insertion [21]. Lu reported that both oestrogen and progesterone receptors decreased significantly after 6-9 months of LNG-IUS use. By down regulation ER in these foci, it may prevent further stimulation by oestrogens, leading to atrophy and shrinkage of endometrial tissues [23].

Prolonged and irregular spotting and bleeding, although in low amounts, during the early months of treatment is the main disadvantage of the LNG-IUS. Patients with menorrhagia are satisfied with reduced bleeding and are not concerned about the side effects. Prolonged spotting or a small amount of bleeding is more tolerable than heavy bleeding every month. In addition, along with the reduction of MBL, the LNG-IUS has the beneficial effect of increasing blood hemoglobin and whole body iron reserves. Although most patients were used to a low level of iron during the long duration of heavy bleeding, they were not in a healthy condition and additional diseases would worsen their condition. Hence, an increase in body iron reserves is important to women’s health in general. For years, these patients had been tired and depressed. It is a great relief to such women when scanty or no bleeding occurs. Regarding younger women, they do not have to worry about accidental pregnancy because they know that the LNG-IUS is also a good contraceptive.

Some women experienced some minor side effects, such as lower abdominal pain, headache, backache, weight gain and breast tenderness, which were negligible when compared with the previous heavy bleeding. In addition, treatment with the LNG-IUS saved the cost, both physically and financially, of surgical intervention, which had been the usual solution when medical treatment failed [22].

As reported by Marjoribanks et al. [23] and Milsom [24] most of the patients of both studies cancelled their decision to undergo surgery and refused to do hysterectomy after using the LNG-IUS for 6 months. There is no doubt that women would be happy to use a device that can stop bleeding as a conservative alternative to hysterectomy. Taking into consideration the total costs of hospitalization, operation, and the postoperative recovery period, one LNG-IUS that can last over 5 years is indeed an excellent method of treatment of menorrhagia.

Hurskainen et al. [15] reported the results of a randomized study comparing the LNG-IUS (119 patients) with hysterectomy (117 patients) in the treatment of menorrhagia in terms of the quality of life and cost-effectiveness. They found that the health-related quality of life improved significantly in both the IUS and hysterectomy groups, as did other indices of psychological well-being. Overall, costs were about three times higher for the hysterectomy group than for the IUS group. The result may not be the same in developing countries. The cost of hysterectomy may be 10 times higher, including all the expenses of hospitalization. For a patient of low socioeconomic status it would be a great burden to the whole family. Even for a minor operation such as endometrial ablation there is no comparison with LNG-IUS insertion as regards cost and safety [16]. Hence, a device that can be an alternative to surgical intervention will certainly be welcomed by many women, especially those in developing countries, where medical care and operations are not available or affordable.

The LNG-IUS is associated with low risk of infection, high continuation rate, and significant reduction of menstrual bleeding [20].

The cases of total and partial expulsion of the IUS in this study could be due to one of two factors:
Heavy bleeding and uterine contraction that causes “flushing out” of the device or descent of the IUS when withdrawing the inserter during the insertion procedure. Therefore, special attention must be paid to proper training of service providers in the insertion technique, and women must be warned of the possibility of expulsion when MBL is over 150–200mL. Checking at the clinic if bleeding is still heavy after the first or second menstrual period is necessary, and a new IUS could be inserted if expulsion has occurred.

Some women may not be willing to tolerate the irregular bleeding that sometimes occurs in the initial phase after LNG-IUS insertion. Hence, counseling before insertion and during follow-up visits about the possibility of irregular bleeding can reassure the patient that bleeding will eventually stop and that reduction of bleeding is beneficial to her health in general.

Today, the LNG-IUS is the most effective medical therapy for menorrhagia unrelated to intrauterine pathology. Intrauterine administration of levonorgestrel has also been shown to be effective in opposing the proliferative effect of oestrogen on the endometrium during oestrogen replacement therapy.

The LNG-IUS may constitute an innovative, effective, safe and convenient alternative for local delivery of a potent progestin in the long-term therapy of recurrent menorrhagia. The use of the LNG-IUS may thus represent a real advance in the treatment of menorrhagia in women who do not want children.

Conclusion:

LNG-IUS reduced MBL with the increase in hemoglobin and serum ferritin levels in women with idiopathic menorrhagia, the patient acceptance and satisfaction was high. Main problem was intermenstrual bleeding. If patients can be counseled before insertion, continuation rates can be high. This treatment is cheaper and more effective than current medical therapy for women with menorrhagia who want to retain their fertility and avoid high risk surgery.

References


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