Review Article

# Mirena: Just a contraceptive device? or A modality with diverse clinical applications !

**Neha Agarwal[1], Seema Chopra[2]**

*[1]Department of Obstetrics and Gynaecology, Maulana Azad Medical College, Lok Nayak Jai Prakash Hospital, New Delhi,*
*[2]Department of Obstetrics and Gynaecology, Post Graduate Institute of Medical Education and Research, Chandigarh, India*

## Abstract

Abnormal uterine bleeding is the most frequently encountered complaint of the reproductive-age women. Heavy menstrual blood loss is responsible for interfering with women's physical, emotional, social, and quality of life. Levonorgestrel-releasing intrauterine device (LNG-IUS) is a highly effective reversible form of contraception. Besides this, its role in the treatment of heavy menstrual bleeding (HMB), endometrial hyperplasia, early-stage endometrial cancers, and endometrial protection as a part of hormone replacement therapy (HRT) is very well studied. This review will revisit the role of LNG-IUS as a nonsurgical option in the management of HMB.

**Keywords:** Abnormal uterine bleed, heavy menstrual bleed, hormone replacement therapy, levonorgestrel-releasing intrauterine device, Mirena

## Introduction

One of the most frequently encountered ailments in the gynecology office is abnormal uterine bleeding. (AUB). The worldwide prevalence of AUB among the reproductive age group is 3%–30%.[1]

It affects 17.09% of Indian women of reproductive age.[2] The International Federation of Gynecology and Obstetrics (FIGO) nomenclature summarizes the parameters for the characterization of normal and abnormal limits of menstruation [Table 1].[1]

In the revised nomenclature, FIGO has adopted the definition of heavy menstrual bleed proposed by the National Institute for Health and Clinical Excellence (NICE) as "excessive menstrual blood loss, which interferes with a woman's physical, social, emotional, and/or material quality of life."[3] On the contrary, the American College of Obstetrics and Gynecology (ACOG) defines heavy menstrual bleeding (HMB) quantitatively as lasting for >7 days and/or loss of >80 mL of menstrual blood per cycle.[4] NICE and FIGO endorse HMB as a symptom rather than a diagnosis.

HMB is largely responsible for jeopardizing a woman's social, personal, and professionallife.[5] It is an important cause for the iron-deficiency anemia encountered in women of reproductive age. Historically, hysterectomy was once considered to be the mainstay treatment for women with heavy menstrual bleeding. However, with advancements in pharmacological methods and with the use of medical methods, it is possible to avoid hysterectomy and associated complications. With this aim, the present review will revisit the role of Mirena as the first line of management of the heavy menstrual bleed.

**Address for correspondence:** Dr. Seema Chopra, Additional Professor, Department of Obstetrics and Gynaecology, Post Graduate Institute of Medical Education and Research, Chandigarh - 160 012, India.
E-mail: drseemachopra@yahoo.com

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**Table 1: FIGO AUB System 2. Nomenclature and definition of AUB symptoms (2018)[1]**

| PARAMETERS | NORMAL | ABNORMAL |
|---|---|---|
| Frequency | 24-38 days | Absent Frequent (< 24 days)<br>Infrequent (> 38 days) |
| Duration | < 8 days | Prolonged (> 8 days) |
| Regularity (Shortest to longest cycle variation) | 7-9 days | Irregular (variation >8-10 days) |
| Flow volume (patient determined) | Normal | Light<br>Heavy |
| Intermenstrual bleeding | None | Random Cyclical/predictable |
| Unscheduled bleeding on Progestin and/or Estrogen Gonadal steroids | Not applicable<br>None | Present |

## Methodology

A comprehensive search of the literature related to levonorgesterol-releasing intrauterine device was undertaken using electronic databases such as PUBMED, MEDLINE, and Google Scholar. Keywords were conducted for publications since 1990 or later non-contraceptive uses of levonorgesterol-releasing intrauterine system.

## Levonorgesterol-Releasing Intra-Uterine System (LNG-IUS; Mirena®): History, and Description

The origin of LNG-IUS dates to 1970 where it was initially developed as a contraceptive device. However, its noncontraceptive benefits have now been well established and used widely in the management of endometriosis, adenomyosis, leiomyoma, endometrial hyperplasia, and fertility-sparing option in early-stage endometrial cancers. LNG-releasing IUS (LNG-IUS) has been approved in 120 countries worldwide for contraception and in 115 countries for the management of heavy menstrual bleed.

Mirena is a T-shaped intrauterine polyethylene device that is 32 mm in length and 32 mm in breadth. A T-shaped body is compounded with barium sulfate which makes it radiopaque. It has a cylinder on its vertical stem which contains a mixture of 52 mg of levonorgestrel and polydimethylsiloxane in a ratio of (1: 1). This cylinder is shielded with polydimethylsiloxane which acts as a control for the release of LNG from the device. LNG is released at a rate of 20 mcg/day for the first 5 years and after that its release is limited to 11 mcg/day.[6] Two monofilament polyethylene threads are attached at the lower end of the vertical stem.

Levonorgesterol, a potent 19-nortestosterone derivative progestin, present in Mirena is systemically absorbed and is detected within 15 min of its insertion. A plateau of 150–200 pg/mL is achieved in few weeks which slowly declines over a period of 5 years. Serum levels are not sufficient to suppress ovulation as that would require levonorgestrel to be released at a rate of 52 mcg/24 h.[7] Levonorgesterol is continually released from the cylinder and is rapidly absorbed locally in the endometrium. This high local concentration of LNG is responsible for atrophy of the endometrial glands and decidualization of the stroma.[8] LNG creates an estrogen-deficient environment leading to endometrial thinning.[9] Vascular changes mediated by LNG include thickening of uterine arteries, suppression of spiral arteriole formation, and capillary thrombosis. The immediate and intense suppression of endometrium can reduce both the duration and amount of menstrual blood loss.[10] The histological changes develop in the first month after insertion and persist until the device is removed.[11] Sonographic changes in the endometrial vasculatures include a reduction in the flow of spiral artery with a decrease in endometrial thickness, as reported by Zalel *et al.*[12] in 75% LNG users. Haliloglu *et al.*[13] also demonstrated an increase in the resistance index of the uterine arteries of LNG users.

## Use of LNG-IUS in Specific Conditions Related To Heavy menstrual Bleeding (HMB)

### LNG IUS in adenomyosis-related HMB

Adenomyosis is a disorder affecting women in the 40s to 50s age group. It is characterized by HMB, dysmenorrhea, and intermenstrual bleed. Fedele *et al.*[14] demonstrated improvement in hemoglobin, hematocrit, and serum ferritin at the 1-year interval after insertion of levonorgestrel intrauterine device (drug delivery: 20 ug/day) in 25 women with HMB secondary to adenomyosis. A prospective study was done in Russia including 180 women to assess the role of LNG- IUS in alleviating the pelvic pain associated with adenomyosis. Pain assessment was done using a visual analog score (VAS). The study was completed by 178 patients and perception of pain improved significantly ($P < 0.01$) at the end of 1 year.[15]

A large prospective study was done by Lie *et al.* to review the effects of LNG-IUS in the management of symptomatic adenomyosis among 1100 women aged 18–45 years. The primary objective was to study the pain relief assessed by visual analog scale (VAS) and visual rating scale (VRS), and decrease in heavy menstrual blood loss assessed bypictorial blood assessment chart (PBAC) score. The secondary objective was to evaluate changes in uterine volume; changes in serum levels of cancer antigen-125 (CA125; with reference <35 ku/L); LNG retention status. Among 1100 eligible patients, 640 patients complained of severe dysmenorrhea, and 618 presented with heavy menstrual blood loss. After 36 months, there was an improvement in PBAC score and hemoglobin level and within 48 months of usage, VAS

and VRS improved, and a progressive decrease in uterine volume and CA- 125 was also found.[16]

Chen *et al* studied the efficacy of Mirena in various types of adenomyosis. They found that efficacy of Mirena was related to the uterine size prior to the insertion of the device and amount of bleeding after its insertion.[17]

Song *et al* studied the prolonged use of Mirena in adenomyosis. Mirena was effective in decreasing the symptoms related to adenomyosis within one month of placement until 6 years. Side- effects related to its use also decreased when used for longer than 5 years.[18]

### LNG- IUS in fibroid-related HMB

Uterine leiomyomas are the most common occurring benign tumors in the reproductive age group. Depending on the size and location of the fibroid, women may have pelvic pain, heavy menstrual bleeding, urinary or bowel symptoms. Socolov *et al*.[19] have well documented the role of LNG- IUS in decreasing the amount of blood loss and reduction in uterine volume.

A study done in the Indian population has provided promising results in combating the blood loss and reducing the uterine volume in patients using Mirena at 48 months of follow-up by 99.5%.[20] However, both studies were not able to find any significant decrease in the size of fibroids.

NICE advocates the use of Mirena as the first-line management in controlling heavy menstrual blood loss secondary to fibroids provided, they are less than 3 cm in diameter and do not distort the uterine cavity.[3]

### LNG- IUS in endometrial hyperplasia

The WHO classifies endometrial hyperplasia into two categories[21]:

(1) Hyperplasia without atypia
(2) Atypical hyperplasia/endometrial intraepithelial neoplasia (EIN).

This classification is done to stratify the disease progression to malignancy. A randomized controlled trial was done in Norway to investigate the effectiveness of LNG-IUS in the management of low- and medium-risk endometrial hyperplasia. All women treated with intrauterine LNG had normal endometrium after 6 months of completion.[22] LNG-IUS is a promising tool in the management of endometrial hyperplasia. A prospective study was done in the UK to evaluate the role of LNG-IUS in endometrial hyperplasia. Their study concluded that regression occurred in 92% of nonatypical and 67% of atypical hyperplasia.[23]

### LNG- IUS in bleeding disorders and patients on anticoagulation (OAC) therapy

One of the common complaints encountered in women with inherited coagulopathies is heavy menstrual bleeding. Von Willebrand disease type 1 is the most common inherited bleeding disorder, and its prevalence is 1%[24] Sixteen women with an inherited bleeding disorder, initially refractory to medical management were treated successfully with LNG-IUS in London.[25] An improvement in pictorial blood loss assessment chart, hemoglobin, and quality of life was observed in 26 patients with inherited bleeding disorder following LNG-IUS insertion in a pilot study conducted in North London.[26] One of the minor complications faced by women on anticoagulants is heavy menstrual blood loss.

Pisoni *et al*.[27] in a systematic review of levonorgesterol as a treatment of heavy menstrual blood loss in patients on anticoagulants concluded that levonorgestrel is an effective alternative to hysterectomy.

## Comparative Effectiveness of LNG-IUS in Treating HMB vs Other Modalities

### LNG- IUS vs other medical therapy

A comparative study was conducted in the UK to study the effectiveness of LNG-IUS vs other forms of medical management including both hormonal and nonhormonal agents. A total of 571 women with HMB were randomly assigned into two groups. One group received levonorgesterol-containing intrauterine devices, whereas the other group received other medical management such as tranexamic acid, mefenamic acid, oral progesterone, or combined estrogen and progesterone. Improvement in the symptoms was assessed by Menorrhagia MultiAttribute Scale (MMAS). This score was obtained after taking practical difficulties – social life, psychological wellbeing, physical health, work routine, and family life into consideration. An improvement in the score was observed in both the groups in 6 months and was maintained for 2 years. This improvement was significantly greater in the LNG-IUS arm than the usual treatment arm.[28] Milsom *et al*.[29] concluded that reduction in blood loss following use of tranexamic acid, a non-steroidal anti-inflammatory drug (flurbiprofen), tranexamic acid, and levonorgestrel- IUS for 12 months was 21%, 44%, and 96%, respectively.

A randomized controlled trial was done by Irvine and colleagues where 44 women with idiopathic heavy menstrual blood loss were divided into two arms. A total of 22 women had levonorgestrel inserted within 7 days of menses, and 22 women received norethisterone from day 5 to day 26 of menses for three cycles. Only 36 women completed the trial, and major dropouts were from the norethisterone group. Although both the arms reported significant improvement in reduction of blood loss, the norethisterone treatment group was less satisfied and less acceptable than the LNG-IUS group.[30]

ECLIPSE trial showed significant difference in improvement of HMB with LNG-IUS compared to other medical methods over 2 years. However by 5 years there was no significant difference between the two groups and surgery rate was also similar.[31]

## LNG -IUS vs endometrial ablation

A systematic review was done by Kauntiz *et al*.[32] where the effectiveness of LNG-IUS was compared to endometrial ablation. They included six randomized controlled trials among which three compared first-generation ablation techniques with LNG-IUS and the other three compared second-generation ablation techniques with LNG-IUS. Both ablative techniques as well as LNG-IUS was successful in decreasing blood loss. The results were comparable in terms of improvement in quality of life as well as a failure of the treatment. LNG-IUS has an added advantage of contraception, whereas ablation has been associated with complications in future pregnancy such as morbidly adherent placenta and uterine rupture.[33] Hence, ablation should only be reserved for women who do not wish for future conception.

Similarly, Soysal *et al* documented endometrial ablation superior to LNG-IUS in decreasing the blood loss with favourable side effect profile at 1 year of usage.[34]

Contrary to this, a 5 year follow up study showed improvement in symptoms, patient satisfaction and low rate of hysterectomy with LNG-IUS compared to ablation.[35]

## LNG-IUS vs hysterectomy

Hysterectomy has been historically considered to be the definitive management of HMB. However, advances in medical sciences have been extremely helpful in avoiding it. In 2004, Hurskainen *et al*.[36] conducted a randomized controlled trial in which the participants experiencing heavy blood loss were randomly assigned to the LNG-IUS group and hysterectomy group. Quality of life and cost were compared between the two groups. Improvement in quality of life was similar in both the groups, but with low cost in the LNG- IUS group.

Llahteenmaki *et al*.[37] performed a study in which they gave the women scheduled for hysterectomy option of insertion of LNG-IUS in the waiting period. The waiting period of surgery was approximately from 1 to 2 years. Among the women with the option of insertion of LNG-IUS in the waiting period, 64.3% of women canceled their surgery following 6 months of treatment, whereas only 14.3% canceled the surgery in the control group.

Spencer *et al* showed superior quality of life with low cost with Mirena compared to the hysterectomy for heavy menstrual bleeding.[38]

# LNG-IUS Use in Hormone Replacement Therapy (HRT)

Hormone replacement therapy remains the most effective therapy for the management of vasomotor symptoms during menopause.[39] Unopposed estrogen replacement therapy poses an increased risk of endometrial hyperplasia and cancer; hence, progesterone should be added along with estrogen replacement therapy (ERT) in women with the uterus *in situ*.[40]

**Studies in perimenopausal women:** When treating the vasomotor symptoms in perimenopausal women, contraception and changes in the menstrual pattern need to be taken into consideration. A prospective trial was carried out in London to study the 5-year efficacy of LNG-IUS on preventing endometrial hyperplasia during estrogen replacement therapy (ERT) in perimenopausal women. By the end of 5 years, not even a single case of endometrial hyperplasia was reported, whereas nonproliferative endometrium was diagnosed in 95.2% of the patients. Improvement in vasomotor as well as psychological symptoms was documented.[41]

Boon *et al*.[42] did a comparative study where perimenopausal women on HRT received continuous estrogen with either LNG-IUS or cyclical progesterone. Cyclical progestin results in secretory changes, whereas continuous LNG-IUS results in endometrial atrophy. Hence, histological findings were not comparable between the two groups but more importantly, none of the groups had hyperplastic changes in the histology. A total of 62% of the women became amenorrhoeic in the LNG-IUS arm, whereas 70%–80% in the cyclical HRT arm resumed normal regular menses.

Studies in postmenopausal women: A 3-year prospective study was done by Sturdee *et al*.[43] where a smaller version of LNG-IUS, menopause levonorgestrel system (MLS) was used. MLS has been specially designed for use in menopausal women in whom cervical stenosis and small uterus can make insertion of the regular LNG-IUS device difficult. Among 294 postmenopausal women, MLS was inserted in 94% at the first attempt. Estrogen was given in the form of a transdermal patch. At the end of 3 years, 87% of the patients did not experience any sort of bleeding and endometrial thickness was below 4 mm in all patients [Table 2].

# LNG-IUS Present and Future Considerations

Studies have shown excellent results with the use of LNG-IUS. The side effects related to its use are the main reason for discontinuation. A retrospective questionnaire was filled by 104 LNG- IUS users where it was inserted as a treatment of heavy menstrual bleed, mode of contraception, and a part of HRT. Out of them, 54% had the device *in situ*, whereas 46% had it removed prematurely. The reason for discontinuation of the drug were unscheduled bleeding (32%), progestogenic side effects (13%) (weight gain, hypertension, edema), and abdominal pain (15%).[46] The diverse role of LNG-IUS in the management of different gynecological pathologies is well proven. However, the side effects associated with it limit its usage. Effective counseling must be done before the insertion of IUD to avoid the premature removal of the device. More information regarding the changes in the menstrual bleeding pattern will help them prepare mentally to accept the device.

**Table 2: LNG studies to assess endometrial protection during HRT in peri and postmenopausal women**

| References | Study Group | Treatment | Endometrial Suppression | Bleeding pattern | Relief of vasomotor symptoms | Drop out | Adverse Effects |
|---|---|---|---|---|---|---|---|
| Hampton *et al.*[41] | 82 perimenopausal | LNG-IUS + oral continuous estrogen | 96-98% non-proliferative endometrium | 93% amenorrhea | Relief of symptoms | 26% drop out | Abdominal pain Mastalgia |
| Boon *et al.*[42] | 200 perimenopausal women | LNG-IUS + oral estrogen vs cyclical combined estrogen + progesterone | LNG grp: 100% Oral grp: 6% | LNG grp: Initial cycles spotting, 62% amenorrheaOral grp: 70%-80% normal cycles | - | 18% drop out from LNG-IUS group | Both grp: Headache Mastalgia Abdominal pain |
| Raudaskoski[44] | 40 postmenopausal women | LNG-IUS + transdermal estrogen vs continuous oral estrogen + progesterone | Comparable endometrial suppression | Spotting was more common in the initial 3 months in the LNG group after that menstrual pattern was comparable | Comparable relief of symptoms in both group | 12% drop out from LNG-IUS group | LNG grp: Abdominal pain Oral Grp: Headache Mastalgia |
| Wildemeersch *et al.*[45] | 83 perimenopausal 58 postmenopausal | Fibroplant LNG + transdermal estrogen | Effective endometrial suppression (TVS) | Perimenopausal grp: 64% amenorrhea Postmenopausal: 100% amenorrhea | - | 7% postmenopausal women drop out 6.8% perimenopausal women drop out | Bloodstained discharge |

## Relevance of this Paper to Primary Care Physicians

A primary care physician (PCP) is the first level of contact in a health care system. Most of the women of reproductive age group are not able to seek specialist care for various constraints. Abnormal uterine bleeding is the most common gynecological problem among women of this age group. Intrauterine system, levonorgesterol is now recommended as the first line of modality in treating this condition. Hence, primary care practitioners should be well versed with the benefits, myths, and side effect profile of levonorgesterol-releasing device. It is a long-acting method, needs one-time interaction with the physician, and has other benefits such as contraceptive and prevention of anemia. This review is an attempt to include not just the contraceptive benefit but also the noncontraceptive benefits of Mirena. Primary care doctors can counsel the patients regarding the use of this device and thus avoiding the need for radical surgical procedures like hysterectomy.

Mirena has been advocated in the use of varied gynecological conditions including endometriosis, adenomyosis, contraception, endometrial hyperplasia, fertility preservation in young patients with early-stage endometrial cancer. Hence, family practitioners and gynecologists should be aware of its myriad uses, side effects, and method of insertion.

## Conclusion

Mirena is an LNG releasing intrauterine device with multiple advantages. It reduces the duration and amount of abnormal menstrual bleeding and significantly decreases pain associated with benign pathologies such as adenomyosis, fibroids, and endometriosis. It offers a role in definitive management in endometrial hyperplasia without atypia. It has fewer adverse effects as compared to systemic progesterone. Hence, the use of MIRENA may be advocated to women of all ages.

## Key Points

a. Mirena is considered as first-line management in the treatment of heavy menstrual bleeding.
b. It has a pivotal role in decreasing menstrual blood loss, increasing the hemoglobin level, and decreasing the uterine volume.
c. It has a role in providing progesterone support in the postmenopausal women as a part of HRT in non-hysterectomized women.
d. Its side effect profile of irregular bleeding/spotting in the initial few months is the main hindrance to its use. Family practitioners can play a vital role in effective counseling as they encounter the patients before an ob-gyn specialist. Later, amenorrhea is the beneficial effect of this device.

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## Conflicts of interest

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