

Levonorgestrel intrauterine system: Current role in management of heavy menstrual bleeding

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ABSTRACT

A review of literature was conducted to report on the effectiveness of levonorgestrel intrauterine system (LNG-IUS) in women with heavy menstrual bleeding (HMB). The relevant data were obtained by computerized searches of PubMed up to December 2012 and other references available with the authors. Information was obtained from references listed. Studies and case reports were excluded if they did not specifically provide information about LNG-IUS usage in women with HMB. After perusal, each relevant publication was summarized and appraised in terms of whether it contained information relevant to the stated objective. Available data shows that LNG-IUS therapy is effective and safe, providing significant reduction of menstrual bleeding in patients with HMB. LNG-IUS is a good strategy to reduce the number of hysterectomies in women with HMB.

Key Words: AUB, heavy menstrual bleeding, hysterectomy, levonorgestrel intrauterine system, menorrhagia, mirena, skyla

INTRODUCTION

Heavy menstrual bleeding (HMB), also commonly called menorrhagia, is menstruation at regular cycle intervals but with excessive flow and duration. Clinically, it is defined as a total blood loss of more than 80 mL per cycle or a period of menses lasting for more than 7 days.^[1] HMB is a common cause of iron deficiency anemia and affects quality of life (QOL) of women. Women with HMB face ebbed QOL, lose work productivity, and consume expensive medical resources.^[2] It is a symptom of several different underlying conditions, which have been recently classified by the Menstrual Disorders Working Group of the International Federation of Gynecology and Obstetrics.^[3] Although hysterectomy is considered the “definitive” cure, many nonsurgical options are also available and allow a woman to retain her ability to bear children and avoid a surgical intervention. Better characterization of the relative efficacy of commonly used nonsurgical therapies will allow for improved patient counseling, facilitate informed decision-making, and reduce the burden of unnecessary

procedures for both the patient and the health-care system. In the present review, we shall focus on role and the present day position of levonorgestrel-releasing intrauterine system (LNG-IUS) in the management of HMB.

HMB: Problem statement

About 30% of the women consider their menstruation to be excessive.^[4] There is plentiful discordance between objective measures of menstrual blood-loss and women’s perception of the amount of bleeding.^[5] Only about half the women with menorrhagia who present to health-care providers have blood loss greater than the traditional clinical threshold of 80 ml per menstrual cycle. Clinical guidelines^[6] now advocate a shift in emphasis from the amount of menstrual blood-loss to the more patient-centered definition of HMB that affects a woman’s physical, social, and emotional life. Harlow, *et al.*^[7] reported excessive bleeding in about 8-9%

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women from India and neighboring countries. In a recent study conducted in South India,^[8] it was reported that 42-53% of women in the two age categories, < 21 years and > 21 years, respectively, complain of excessive bleeding. However, an earlier study by Sanyal, *et al.*^[9] reported an occurrence of large variations in menstrual bleeding among 23.5% women from West Bengal.

Levonorgestrel-releasing intrauterine system: Evolution

The history of the intrauterine devices (IUD) is curiously petite, albeit interesting; with its existence endangered several times. It indeed started with Ernst Gräfenberg, a German, who was first to introduce the intrauterine ring in 1928. He felt that “A satisfactory contraceptive method is the most important in dealing with psychosexual disturbances in women. By removing fear and the necessity for objectionable preparations, many physical and mental inhibitions are removed.” However, virtually all leaders of German gynecology denounced him and his thoughts, and intrauterine contraception was labeled as a medically unacceptable method of birth control. Shortly thereafter, Nazi regime proclaimed contraception to be a threat to the physical and mental-health of Aryan women. With this, advertising of contraceptives and/or contraceptive advice became illegal in Germany and the other Axis States. Gräfenberg was debarred from practice and research, shunned by his colleagues and hounded by the authorities. He left Germany in 1940 and went to New York. Although at that time even in America acceptance of contraception was not there, still, Gräfenberg presumably transgressed medical rules and continued to use the intrauterine ring in secret and in his private practice. However, he was immortalized in a history of human sexology when he described the vaginal erogenous zone in 1950, and which is called the ‘G-spot’ after him.

In the 1980s, cynicism about the IUD was based on the datum that there are still two major limitations fundamental in intrauterine contraception: Its lack of protection against both ‘*gynae*’ and sexually transmitted diseases. Let’s accept that bilateral monogamy is the first pre-requisite for the safe use of this method of contraception, and it can in no way protect from sexually transmitted diseases. However, the second drawback, i.e., the lack of so-called ‘*gynae*’ protection, was the one, which was targeted. It was menorrhagia, which was a nuisance to IUD usage, and bleeding problems were and still remain the most frequent single reason for the removal of an IUD. Consequently, research concentrated on the alleviation of abnormal vaginal bleeding. It was presumed that bleeding was related to endometrial trauma caused by the geometric incompatibility between the frame of IUD and the uterine cavity, and consequently it was logical for research to

concentrate on this factor. It was thought that since uterine cavity, when contracted, assumes the shape of a capital ‘T’, a small T-shaped IUD would solve these problems. However, even the copper-bearing T-shaped devices did not solve the menorrhagia problem. In the late 1960’s, Antonio Scommegna demonstrated the uterine effects of progesterone and hypothesized that the endometrial atrophy elicited by progesterone would be useful in preventing implantation and reducing menstrual bleeding. He envisioned a plastic, T-shaped IUD, the vertical arm of which was replaced by a reservoir filled with crystalline progesterone. The Progestasert System (Alza Corporation) was marketed in 1976, but never gained wide popularity for the short (1-year) effective lifespan it had.

Dr. Jouni Valter Tapani Luukkainen, the creator of the Nova-T IUD (a copper-T device with flexible arms) had initiated his quest for a long-acting steroid-medicated IUD in the early 1970s. The Ng Nova-T materialized in 1976, a Nova-T IUD from which the copper filament had been removed and the vertical arm replaced by a small reservoir releasing a constant daily dose of 20 µg levonorgestrel (Ng) over a period of at least 5 years. It was finally in 1977 that the first serviceable gestagen IUD was introduced. This LNG-IUS was commercially named Mirena.

Levonorgestrel-releasing intrauterine system: Current status

Since HMB is a subjective finding, its treatment regimens should address specific aspects of the menstrual cycle that seem to be abnormal, such as cycle length or quantity of bleeding. The guidelines from the National Institute for Health and the Clinical Excellence^[6] recommend the use of LNG-IUS in women with benign HMB. If bleeding was not controlled with medical management, endometrial destruction was recommended to resolve symptoms. The surgical options include conservative surgery and hysterectomy. However, LNG-IUS has been shown to provide a non-surgical alternative, which is reversible and spares fertility.^[10]

Evaluation of the efficacy of therapies for HMB has evolved from a focus merely on quantity of bleeding to one focused on patient-based outcomes as well especially, measures of QOL. Clinical guidelines^[11] recommend the use of patient-based outcome measures because these measures capture the effect of heavy bleeding on women’s psychological and physical well-being. Comparative studies have established the superiority of the levonorgestrel-IUS over other treatments in reducing blood loss in women with HMB.^[12]

Rationalized meta-analyses, including the results of nine randomized trials (involving a total of 783 women)

of LNG-IUS as compared with non-hormonal and hormonal treatments, showed that the LNG-IUS resulted in a greater reduction in menstrual-blood loss at 3-12 months of follow-up.^[13] Nevertheless, it was unclear whether these short-term benefits endure, particularly since the discontinuation rate of LNG-IUS are as high as 28% at 2 years,^[14] and the effects of this therapy on bleeding-related QOL were unknown. Recently, results of The effectiveness and cost-effectiveness of levonorgestrel-containing intrauterine system in primary care against standard treatment for menorrhagia (ECLIPSE) trial^[15] were published in The New England Journal of Medicine (NEJM). ECLIPSE was a pragmatic, multicenter, randomized trial that compared the clinical effectiveness of the LNG-IUS with that of usual medical treatment (tranexamic acid, mefenamic acid, combined estrogen–progestogen, or progesterone alone) in the primary care setting. The trial has added strong evidence that LNG-IUS improves QOL more than the usual medical treatments do for this condition. Indeed, the accompanying editorial^[16] also clinched “the results demonstrate that the LNG-IUS should be considered as the first-line therapy for HMB, regardless of the need of contraception.”

Furthermore, the Systematic Review Group of the Society of Gynecologic Surgeons recently conducted a systematic review with the goal of producing an evidence-based guideline on nonsurgical treatment decision-making for abnormal uterine bleeding presumed secondary to ovulatory dysfunction and to endometrial dysfunction. It was published in the Green Journal (Obstetrics and Gynecology)^[17] reaching a conclusion that for the reduction in mean blood loss in women with HMB presumed secondary to abnormal uterine bleeding presumed secondary to endometrial dysfunction, use of the LNG-IUS is recommended over OCPs, luteal-phase progestin’s, and NSAIDs.

LNG-IUS: Posology

Levonorgestrel is a potent progestin of 19-nortestosterone. LNG-IUS (Mirena, Bayer Health-care AG) consists of a T-shaped polyethylene frame (T-body) with a steroid reservoir (hormone elastomer core) around the vertical stem. The reservoir consists of an almost white cylinder made of a mixture of levonorgestrel and silicone (polydimethylsiloxane), containing a total of 52 mg levonorgestrel. The reservoir is covered by a semi-opaque silicone membrane. The T-body is 32 mm in both the horizontal and vertical directions. The polyethylene of the T-body is compounded with barium sulfate, which makes it radiopaque. A monofilament brown polyethylene removal thread is attached to a loop at the end of the vertical stem of the T-body [Figure 1].

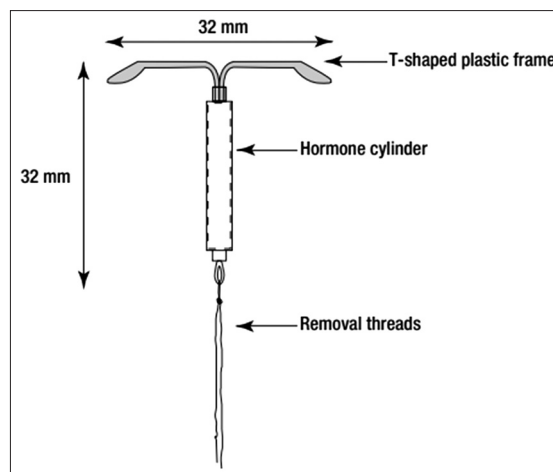


Figure 1: Schematic illustration of levonorgestrel intrauterine system

The LNG-IUS releases a therapeutic daily dose of levonorgestrel (20 µg/day) for 5 years.^[18] The capillary network of the basal endometrial mucosa quickly absorbs intrauterine LNG and measurable levels of LNG have been detected in plasma 15 min after insertion. The peak plasma LNG concentrations of sub-dermal implants are 400 pg/mL, while those with LNG-IUS would correspond to about half the values of implants. Peak plasma LNG concentrations can be detected within a few hours after insertion, which level off at 150-200 pg/mL (0.4-0.6 nmol/L). Levonorgestrel is continuously released from LNG-IUS, which means that there are no ‘peaks and troughs’ in serum LNG levels unlike that of oral progesterone dosing.

LNG down regulates the estrogen and progesterone receptors. The expression of some of the cytokines and the growth factors has been found to show variable responses. The cyclical activity of endometrium is lost after the insertion of LNG-IUS and the endometrium becomes dormant and nonresponsive to estrogen. This change in the endometrium is associated with irregular bleeding or spotting during the initial months of LNG-IUS use.

The LNG-IUS targets the endometrium directly by releasing of LNG. This results in the high local LNG concentrations that cause uniform suppression of endometrial proliferation, inactive histology, thin epithelium, and decidualization of the stroma. LNG-IUS decreases the menstrual blood loss and pain by the suppression of endometrial proliferation.

Kriplani, *et al.*,^[19] evaluated the efficacy, acceptability, and possible side-effects of LNG-IUS for menorrhagia, and concluded that LNG-IUS is an effective and well-accepted option in the medical management of menorrhagia. A significant decrease in the mean number of bleeding days at 1 month was observed in women with menorrhagia, and the decrease continued with treatment duration.

Further on, we shall compare the available data on the LNG-IUS versus other modalities of treatment of HMB and in certain special situations.

Levonorgestrel-releasing intrauterine system: Comparative effectiveness LNG-IUS versus hysterectomy

Hysterectomy is the definitive cure for HMB, however, and then is a major surgical procedure with significant physical and emotional complications along with increased costs. Furthermore, there are less invasive surgical techniques (such as endometrial resection and laser ablation) that can remove the excessive thickness of the endometrium. However, the patients shall be eternally grateful if she can be spared the knife,^[20] and if the resultant outcomes including the QOL after a conservative medical management can be comparable with a surgical treatment.

Subramaniam *et al.*,^[21] who conducted a 1-year follow-up study, reported that 20% of the women who underwent hysterectomy developed the psychiatric problems, mainly depression. Thus, women undergoing hysterectomy need to be counselled so as to prevent the psychiatric complications. Singh *et al.*^[22] have observed that despite reporting relief after hysterectomy, most women have a 'sense of void' and 'loss of womanhood' after the operation. In this study, researchers also noted that 41.25% of the women had early menopause and were categorized as a high-risk group (high serum follicular stimulating hormone). Further, about 21% women who have had hysterectomy and 43% who had hysterectomy with oophorectomy, regretted the loss of fertility after 3 years of the operation.^[23]

Therefore, there are more reasons than one to save a hysterectomy in case the relief can be provided by a conservative medical mode of treatment.

Lahtenmaki *et al.*, conducted a randomized trial^[24] to assess if LNG-IUS could provide a conservative alternative to hysterectomy in the treatment of excessive uterine bleeding. The study included two parallel groups: A LNG-IUS group and a control group, comprising a total of 56 women aged 33-49 years scheduled to undergo hysterectomy for the treatment of excessive uterine bleeding. Researchers reported that at 6 months, 64.3% of the women in the LNG-IUS group and 14.3% in the control group had cancelled their decision to undergo hysterectomy. The study concluded that LNG-IUS was a good conservative alternative to hysterectomy in the treatment of menorrhagia. Hence, the researchers recommended that LNG-IUS should be considered before hysterectomy or any other invasive treatment.

Hurskainen, *et al.*, in a randomized controlled trial^[25] compared outcomes, health related quality-of-life (HRQL),

and cost of the LNG-IUS with hysterectomy in the treatment of menorrhagia ($n = 236$). The study participants were randomly assigned treatment with LNG-IUS ($n = 119$) or hysterectomy ($n = 117$) and monitored for 5 years. According to the researchers, LNG-IUS provides improvement in HRQL at relatively low-cost and may be of choice for the patient by decreasing costs due to interventions involving surgery. Bahamondes, *et al.*, conducted a study^[26] to compare the resources and the procedures involved in inserting an LNG-IUS ($n = 124$) with performing hysterectomy in women with HMB ($n = 122$). At 1-year, HMB was controlled in 83.1% of women in the LNG-IUS group. The study researchers concluded that the LNG-IUS is a good strategy to reduce the number of hysterectomies and resources utilized for women with HMB.

Approximately, one-third of all hysterectomies are carried out in women younger than 35 years of age. According to investigators,^[27] the extent of these unnecessary hysterectomies as well as providers' attitudes required further investigation. According to Singh *et al.*,^[22] 7% married women aged above 15 years undergo hysterectomy, which was significantly more common in those aged above 35 years, mostly for the treatment of HMB. In another study, researchers reported 60% of women who had undergone hysterectomies were less than 30 years of age and the average age at which hysterectomy was done was 24.6 years. It follows that hysterectomy is increasingly being performed in younger women in India. It is associated with the significant physical and emotional complications and increased costs. In such patients, LNG-IUS has been shown to provide improved HRQL and effective bleeding control at reduced costs.^[25]

LNG-IUS versus thermal balloon ablation (TBA)

A prospective, randomised controlled trial compared 5-year follow-ups of LNG-IUS and TBA for the treatment of HMB.^[28] It reported that women treated with TBA had higher rates of hysterectomy (24%) due to treatment failure compared to the LNG-IUS group (3.7%). According to the study LNG-IUS use resulted in higher mean hemoglobin levels in comparison to the TBA group. Further, menstrual blood loss was significantly higher in the TBA when compared to the LNG-IUS group (45.5% vs. 0.0% $P < 0.001$). Researchers also found that the patient acceptability, perceived clinical improvement, and overall satisfaction rates were significantly higher in women using LNG-IUS.

LNG-IUS versus other medical therapies

In a pragmatic, multicenter, randomized trial^[15] researchers compared the LNG-IUS with usual medical treatments in women with menorrhagia. The study involved 571 women with menorrhagia who were given LNG-IUS or

usual medical treatments. The usual medical treatments were tranexamic acid, mefenamic acid, combined estrogen-progestogen, or progesterone alone. The primary outcome, the patient-reported score on the menorrhagia multi-attribute scale (MMAS), was assessed over a 2-year period. Researchers reported that the MMAS scores were improved from baseline to 6 months in both the treatment groups (mean increase, 32.7 [LNG-IUS] and 21.4 points [usual medical treatment] $P < 0.001$). These improvements were reported to be maintained over a period of 2 years; however, the improvement was significantly greater in the LNG-IUS group when compared to the usual-treatment groups (mean between-group difference: 13.4 points; 95% CI: 9.9-16.9; $P < 0.001$). According to the researchers, LNG-IUS treatment provided significantly greater improvements in MMAS for practical difficulties, social life, family life, work and daily routine, psychological well-being, and physical health as compared to the usual-treatment group. At the end of 2 years more women were still using the LNG-IUS compared to those receiving usual medical treatments (64 vs. 38%, $P < 0.001$). Researchers reported that the LNG-IUS was more effective than usual medical treatment in women with menorrhagia for reducing the effect of HMB on QOL.

In a multicenter, randomized study^[29] researchers compared the effects of the LNG-IUS ($n = 82$) with cyclic oral medroxyprogesterone acetate (MPA) ($n = 83$) in women ($n = 165$) with confirmed HMB over six cycles of treatment. According to the researchers, the number of women who rated their bleeding as 'improved' at cycle 6, was higher with the LNG-IUS compared to oral MPA, in both investigator assessments and self-assessments [Figure 2]. The study also concluded that women who were treated with the LNG-IUS had greater increases in median hemoglobin and serum ferritin levels.

Irvine, *et al.*, in a randomized comparative parallel group study^[30] reported that the percentage control of blood loss with LNG-IUS was 94%, and oral norethisterone it

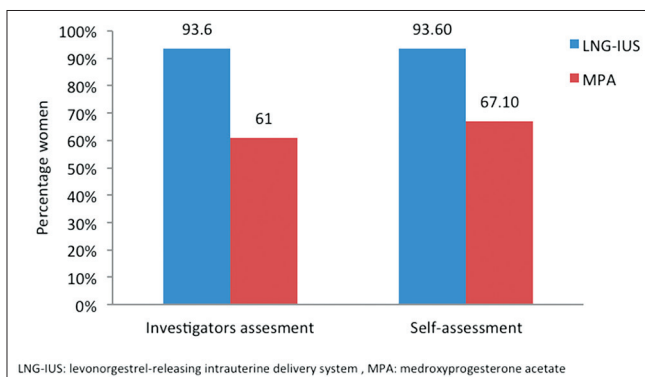


Figure 2: Proportion of women with improved bleeding at cycle 6

was 87%. The researchers opined that LNG-IUS offers an effective alternative to currently available medical treatments for menorrhagia. In an efficacy comparative study of LNG-IUS with that of a low-dose combined oral contraceptive (COC),^[31] it was found that LNG-IUS was more effective in reducing menstrual blood loss than COC in women with fibroid-related menorrhagia. The reduction of menstrual blood loss was significantly greater in the LNG-IUS group compared to the COC group ($90.9 \pm 12.8\%$ versus $13.4 \pm 11.1\%$; $P < 0.001$).

Levonorgestrel-releasing intrauterine system: Efficacy in HMB due to uterine diseases

Kriplani, *et al.*, reported that in HMB associated with leiomyomas,^[32] menstrual blood loss was reduced by 92.1, 97.4, 97.4, 99.5, and 99.5% at 3, 12, 24, 36, and 48 months respectively. A significantly greater reduction occurred in the mean uterine volume in the group with leiomyomas. Socolov, *et al.*,^[33] evaluated the effectiveness of the LNG-IUS in the treatment of frequent irregular uterine bleeding in women with uterine myomas and reported that LNG-IUS was effective in controlling bleeding due to myomas.

Researchers are of the opinion that LNG-IUS is effective and safe in providing long-term relief from menstrual problems in women with adenomyosis.^[34] A study comparing the effects of the LNG-IUS and the copper T380A intrauterine device on menstruation and dysmenorrhea showed a significant improvement in duration of the menstrual bleeding, dysmenorrhea, and hemoglobin in the LNG-IUS treatment group than the other groups.^[35] Another study conducted by Sheng, *et al.*^[36] reported that LNG-IUS use relieved dysmenorrhea associated with adenomyosis in a follow-up period of 3 years.

Levonorgestrel-releasing intrauterine system: Efficacy in women with hemostatic bleeding disorders

Long-term efficacy of LNG-IUS in the management of HMB in women with bleeding disorders has been evaluated^[37] and LNG-IUS has been found to be effective. Lukes, *et al.*, reported that the LNG-IUS in women with hemostatic bleeding abnormality was associated with improved QOL.^[38] Another study^[39] documented that LNG-IUS showed an improvement of menorrhagia in about 68% of the patients with hemostatic disorders. Therefore, researchers concluded that LNG-IUS can be considered over surgery in this population of patients.

Levonorgestrel-releasing intrauterine system: Economics

It has been conclusively proven that LNG-IUS is much more cost effective than a hysterectomy. The medical

management of HMB mainly comprises the use of NSAIDs such as mefenamic acid or the use of antifibrinolytics such as tranexamic acid, or many a times, a combination of these. The advantage of these agents over other modalities is that they can be used only for five to seven days during menstruation and need not be used for the entire month. The usual dose of these agents is thrice daily and the cost of this therapy for each cycle works to around Rs 300 approximately, based on the present average cost of the major brands for these agents in Indian market. Assuming this treatment modality is used for a 5 year period, it would cost Rs 18000. When these therapies are compared to LNG-IUS where the cost of therapy for 5 years works out to around Rs 8500, LNG-IUS appears to be much economical. Also, using monthly medical therapy results in frequent physician visits and resultant cost additions.

Counselling: A key to better prognosis

LNG-IUS is well-tolerated in the treatment of HMB. The adverse effects reported with the LNG-IUS in women with HMB^[12] are similar to those typically observed in women using an intrauterine system for contraception. The use of LNG-IUS has been associated with spotting, intermenstrual bleeding in the first few months of insertion and amenorrhea. A study^[19] reported that the most common side-effect was intermenstrual spotting during the first 6 months, and 28.57% developed amenorrhea.

In a 3-year study,^[40] researchers reported a continuation rate of 90.3% with LNG-IUS and about 97% of women reported alterations in their menstrual pattern, 34% reporting a decrease in the amount of bleeding, 17% had persistent spotting or inter-menstrual bleeding, and 56% reported at least a temporary period of amenorrhea. However, the number of women who were very satisfied with the LNG-IUS increased steadily with the duration of treatment, with 29% after 2 weeks, 56% after 2 months, 69% after 6 months, and 77% after 36 months.

The amount of satisfaction with the use of LNG-IUS has been reported to correlate with how well-informed patients are with regard to possible side-effects associated with it. In a study,^[41] researchers reported that 95% of patients were satisfied with the LNG-IUS. This percentage of satisfied patients increased to 99% among those using their second LNG-IUS. The reasons for using the LNG-IUS included the need for contraception, its high efficacy, and reduced menstrual bleeding. User satisfaction was shown to be associated with the amount of information provided to the patients regarding different symptoms such as menstrual irregularities, pregnancy, and pelvic inflammatory diseases regardless of the specific symptom experienced by them. Backman, *et al.*,^[42] reported that most of the current LNG-IUS users were very or fairly satisfied with it. In

particular, women who were warned of the possibility of amenorrhea were more satisfied than the women who were not, irrespective of them experiencing the symptoms or not.

Levonorgestrel-releasing intrauterine system: What's new?

In January 13, USFDA has approved a new LNG-IUS, Skyla™ (Bayer Health-Care Pharmaceuticals Inc.). It is small, flexible plastic T-shaped device containing 13.5 mg of levonorgestrel. The size of the Skyla T-body is 28 mm × 30 mm and the outer diameter of the placement tube is 3.8 mm. It has a new inserter system that's different than that of Mirena. It would release 14 mcg LNG/day after 24 days of placement and would decline to 5 mcg/day after 3 years. The average *in vivo* release rate of LNG would be approximately, 6 mcg/day over a period of 3 years. Presently, Skyla is approved in USA only for contraception.

CONCLUSIONS

HMB is a frequent and widespread symptom that has an enormous effect on the QOL of women and health-care costs. It is one of the most common reasons for patient visits to gynecology clinics. This review provides a succinct summation of the available evidence on the present day status and efficacy of LNG-IUS in management of this important problem that gynecologists treat on a regular basis. Although there are limitations to the body of literature on this symptom, this review provides up-to-date information on the relative effectiveness of treatments of HMB commonly used in clinical practice and will succor the clinicians with clinical decision-making and also setting primacies for further research on this important symptom. Various therapeutic options are available. The usual medical treatment for women with HMB includes tranexamic acid, mefenamic acid, combined estrogen-progestogen, or progesterone alone. Recent research has conclusively brought out that LNG-IUS is more effective than usual medical treatments in reducing the effect of HMB on QOL.

Hysterectomy remains a definitive cure but then, is a major surgical procedure for the treatment of HMB and it has significant anatomical, urological, sexual, psychological, and emotional sequale attached to it apart from increased costs. Even the uterus sparing conservative surgical techniques are associated with various risk factors. In India, hysterectomy has been reported to be performed in younger age group of patients, who often regret having undergone the procedure. The LNG-IUS therapy is effective and safe, providing significant reduction of menstrual bleeding in patients with HMB and can be considered over surgery. It can be considered as a first line treatment in the management of HMB.

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