THE JOURNAL OF OBSTETRICS AND GYNECOLOGY OF INDIA

The Journal of Obstetrics and Gynecology of India (July–August 2018) 68(4):253–257
https://doi.org/10.1007/s13224-017-1050-z

INVITED MINI REVIEW

Is LNG-IUS the One-Stop Answer to AUB?

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Received: 22 August 2017 / Accepted: 2 September 2017 / Published online: 12 September 2017

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Abstract A systematic search of the literature available on the use of Levonorgestrel intra-uterine system (LNG-IUS) in women with abnormal uterine bleeding was done. This included PubMed searches up to February 2017 as well as references available with the authors. LNG-IUS usage in other situations was not included in the study. Each relevant published article was evaluated as to whether it served the purpose of this review. Available data show that LNG-IUS is certainly the one-stop answer to AUB, providing a safe and cost-effective treatment and being a substitute for hysterectomy in most women with AUB.

Keywords Levonorgestrel intra-uterine system (LNG-IUS) · Abnormal uterine bleeding · Non-surgical management of AUB · Heavy menstrual bleeding · Hysterectomy

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Introduction

Abnormal uterine bleeding (AUB) which includes acute, chronic and intermenstrual types of abnormal uterine bleeding is a common problem among women in the reproductive age group, affecting about 17.9% of the Indian population [1].

The abnormality may be in volume, regularity or timing. The AUB patterns include menorrhagia, metrorrhagia, polymenorrhoea, dysfunctional uterine bleeding and heavy menstrual bleeding (HMB).

In 2011 FIGO introduced the PALM-COEIN system of nomenclature of AUB [2]. The acronym stands for Polyp, Adenomyosis, Leiomyoma, Malignancy and Hyperplasia, Coagulopathy, Ovulatory disorders, Endometrial factors, Iatrogenic and Not defined (or classified).

Many patients come to the gynaecologist only after years of silent suffering from AUB. Several methods of tackling this problem medically and surgically have been tried. FOGSI guidelines for management of AUB were formulated and published in July 2016 with the hope of standardizing clinical practices in India. This was based on good scientific evidence from existing guidelines: Nice [3], ACOG 2013 [4], SOGC 2013 [5], France 2010 [6].

Ever since its launch in 1977, the LNG-IUS has steadily been replacing medication and surgery as a satisfactory management option for women with AUB. A constant search for a suitable alternative to hysterectomy showed that this minimally invasive treatment modality could indeed be a one-stop answer to AUB. Due to its continuous progestogenic effect on the endometrium, it reduces the amount of bleeding by over 90% providing an incredible non-surgical alternative, which is both reversible and fertility sparing, in the treatment of heavy menstrual bleeding.

This minimally invasive technique of treatment of different types of AUB was evaluated for its efficacy. Studies and meta analytic reviews up to 2015 all show the gradual evolution of the LNG-IUS as an effective tool which provides improved quality of life(QOL) and not merely decreases the quantity of menstrual bleeding. The focus is on patient-based outcomes, that is, the psychological and physical well-being of a woman with HMB. Subsequent studies up to February 2017 were also looked into, all pointing to the LNG-IUS as a non-surgical lifeline for AUB.

Discussion

Almost 1 in 5 of the Indian female population suffers from abnormal uterine bleeding (AUB), and since nearly 30% of all hysterectomies are performed to alleviate the problem of HMB [7, 8], a comparison of the effectiveness of LNG-IUS versus other treatment modalities in different types of AUB was made. Safety, patient satisfaction, cost-effectiveness and health-related quality of life, reversibility and fertility sparing effects were different aspects of this comparative study which were evaluated in detail. The LNG-IUS emerged as a winner among the wide array of contestants!

Levonorgestrel-Releasing Intra-Uterine System (LNG-IUS)

After the introduction of the first intra-uterine contraceptive device—the Grafenberg ring in 1928, many changes in the structure, shape and content of the IUCD occurred. The contracted uterine cavity being T-shaped, the T-shaped device emerged as the best of the lot, copper being the favourite content. The problem of menorrhagia was solved by adding progesterone which caused both endometrial atrophy and prevention of implantation. This was suggested in the 1960s by Antonio Scommegna—a T-shaped IUD, the vertical arm of which was replaced by a reservoir of crystalline progesterone. A short-acting LNG-IUS was marketed in 1976. It remained unpopular because of its short lifespan of 1 year. Dr. JVT Luukkainen, the creator of Nova T IUD, was also responsible for the introduction of the long-acting steroid-medicated IUD in the early 1970s. The first serviceable gestagen-IUD came into the market in 1977. This LNG-IUS would release 20 μg Levonorgestrel (LNg) daily over a period of at least 5 years.

Posology of the LNG-IUS

Levonorgestrel 52 mg is contained in the vertical arm of the LNG-IUS. The T body made of polyethylene compounded with barium sulphate is radio-opaque. It releases a therapeutic daily dose of LNG (20 μg per day) for 5 years. The hormone down regulates the oestrogen and progesterone receptors. The endometrium becomes dormant losing its cyclical activity and response to oestrogen. This change is associated with irregular bleeding or spotting during the initial months of LNG-IUS use. High local LNG concentration cause uniform suppression of endometrial proliferation, thin epithelium and stromal decidualization. Thus, LNG-IUS decreases menstrual blood loss and pain by suppression of endometrial proliferation.

The Current Status of the LNG-IUS in the Management of Different Types of AUB

Magnon et al. [9] published their findings after reviewing all studies relating to the use of this device in HMB. Their review was able to prove conclusively that LNG-IUS is more effective than usual medical treatments in reducing the effect of HMB on QOL [10–12]. Surgery, especially hysterectomy while remaining a definitive cure, has significant risk factors. .Anatomical, urological, sexual, psychological and emotional sequelae as well as cost factors are definite drawbacks [13, 14].

In the Cochrane database systematic review 2015 [15], 2082 women in 21 RCTs were included for assessing the use of the LNG-IUS in all kinds of AUB. Comparisons were made with placebo, oral medicines, endometrial destruction techniques and hysterectomy. Though inconsistency and inadequacy of reporting of study methods were limitations in the evidence, the findings showed that QOL and reduction in HMB were more with the LNG-IUS compared with medical and endometrial destruction techniques. Minor adverse events were more (pelvic pain, breast tenderness, ovarian cyst, etc.). Cost-effectiveness was a major plus point for up to 10 years of treatment in a study where LNG-IUS was compared with hysterectomy. High-quality evidence showed that reduction in HMB was not as successful as with hysterectomy.

The Eclipse trial [16], a UK-based multicentric randomized controlled trial, featured the use of LNG-IUS in primary care against standard treatment for menorrhagia. The results were published in 2013 in The New England Journal of Medicine (NEJM) and provided strong evidence that QOL improved with LNG-IUS more than with usual medical methods of treatment. The accompanying editorial in NEJM also said that the results demonstrated that the LNG-IUS should be considered first-line therapy for HMB regardless of the need for contraception [17].

More recently, diagnosis and management of AUB was standardized by the FOGSI Expert Panel meeting held in September 2015. FIGO nomenclature of AUB, that is, the PALM-COEIN system of classification [2], was used. Good clinical practice recommendations (GCPRs) were made based on good evidence from India and abroad. Existing guidelines, meta-analysis, cross-sectional studies, systematic reviews and key-cited articles related to AUB were reviewed by experts [18].

In the management of AUB-PALM, LNG-IUS was recommended as the first-line treatment for benign polyps (post-hysteroscopy), AUB-A in women with adenomyosis desiring fertility but not immediate conception, AUB-L, intra-mural and subserous leiomyoma with immediate conception not required and AUB-M hyperplasia endometrium without atypia.

In AUB-COEIN, coagulopathy had LNG-IUS as second-line treatment of choice. AUB-O and E had similar recommendations, that is, where COC (combined oral contraceptive pill) is contraindicated, LNG-IUS is preferred as first-line treatment. LNG-IUS was also recommended as first-line treatment in AUB-I (Iatrogenic) after change of agent and in AUB-N (not defined) where the woman desired contraception.

Evidence-based management would avoid a number of unnecessary hysterectomies since 25% of all gynaecological surgeries are done for AUB [19].

Further studies both Indian and international have substantiated the evidence-based recommendations made by FOGSI in September 2015. In a 3-year prospective Indian study of 70 women with varying types of AUB where large organic lesions and malignancy was excluded, follow-up for a maximum of 2 years showed 80% reduction in median menstrual blood loss (MBL) which rose to 95% by 1 year and 100% by 2 years [20]. Satisfaction rates were 91.4%. Minor side effects needed reassurance only. Fifty-seven percentage had no side effects .Hysterectomy was needed only for 5.7% proving that the LNG-IUS is an excellent alternative to hysterectomy.

Green Top Guideline No 67 (RCOG-BSGE February 2016, updated in 2017) [21] recommends the LNG-IUS as first-line medical management of endometrial hyperplasia without atypia. In endometrial hyperplasia with atypia in a women desirous of fertility preservation, LNG-IUS is the first-line treatment after counselling about the risks of underlying malignancy or disease progression. Once fertility is no longer required, hysterectomy should be offered. Use of the LNG-IUS is also recommended to protect the endometrium during HRT.

Garg Seeru et al in a 2-year prospective comparative study published in 2016 from Bombay [22] described the LNG-IUS as a non-surgical lifeline for AUB due to its cost-effectiveness and psychological and symptomatic relief achieved in women compared with those who underwent laparoscopic hysterectomy.

George Joy Eralil evaluated the effectiveness of LNG-IUS in treating HMB in a retrospective observational study (2016) of Indian women [23]. The comparison with usual medical treatment methods showed higher satisfaction rates over the course of 2 years with 36% discontinuation rates due to the lack of effectiveness and irregular bleeding. Six percentage resorted to hysterectomy in both groups, proving that LNG-IUS remains the first choice in our population, as assessed by the impact of bleeding on the women's QOL.

Pontis et al. [24] in a systematic review of medical treatment of adenomyosis published in July 2016 spanning a period of 25 years (1990–2015) concluded that LNG-IUS is the most promising medical therapy available with a low profile of adverse effects.

Singh et al. [25] from Patna, India, in a 2-year prospective interventional study on 42 patients published their findings in February 2017. HMB due to causes like malignancy, large fibroids, submucous fibroids, infection, coagulopathy was excluded. LNG-IUS was once again proved to be an acceptable, highly efficient method of reducing menstrual blood loss in women with HMB and a good alternative to hysterectomy in HMB due to benign aetiology. LNG-IUS could be used in the entire

Table 1 Comparison of results of various recent studies on the effectiveness of LNG-IUS in AUB

	References	Follow-up in years	QOL	Decrease in HMB	Rate of discontinuation	Reduction in dysmenorrhoea	Proved cost-effectiveness	Amenorrhoea	Hysterectomy needed	HB levels
1	Magnon et al. [9]	Varying 2–5 years	Improved significantly	Significant	Variable around 28%	Effective	Significant	Almost 100% by 2 years	–	Improved
2	Cochrane Review [15]	–	Improved	Not as successful as hysterectomy	–	Minor side effects more	More cost-effective up to 10 years	Not available	–	Higher
3	Eclipse trial [16]	2	Significant improvement	Significant	53% at 5 years	Significant	Significant—short and medium term		-20% at 5 yrs	Improved
4	Dhamangaonkar [20]	3	91.4% satisfaction rate	80% fall At 4 months 95% at 1 yr	–	Significant	significant	100% at 2 years	–	7.8% rise
5	Pontis et al. [24]	Up to 5 years	68% Overall success	Improved	32%	Improved	–	25%	16.7%	Improved
6	Garg [22]	2	Improved	Improved	–	Improved	Improved	–	–	–
7	Eralil [23]	2	Improved significantly	Improved significantly	36%	Improved significantly	–	–	6% needed surgery	Improved
8	FOGSI GCPR-evidence [18]	5–10 years	Improved	Significant	28% In a significant study	Improved well	Significant	–	–	Increased
9	Singh [25]	2	92.5% satisfied	44.4% achieved scanty menstruation	5% expulsion in 3 months	Improved	Yes	81% in 1 year	–	Improved

reproductive age group and help in a smooth transition to menopause (Table 1).

Conclusion

This review provides the latest information on the relative effectiveness of various treatments of AUB available in clinical practice. It will help with clinical decision-making and set the path for further research.

The LNG-IUS has been used as a substitute for hysterectomy in AUB-PALM ranging from polyp, adenomyosis, endometriosis, endometrial hyperplasia to fibroid uterus, as well as in the non-structural causes of AUB i.e AUB-COEIN. Cost factor has come down (cost has been halved in the Indian market), and proper counselling allows the patient to accept minor initial reactions like spotting and irregular bleeding. A smaller version of the LNG-IUS which now has FDA approval only for contraception may overcome the problem of increased expulsion rate. Its shorter lifespan of 3 years may also work to the advantage of the patient in certain situations like desire for fertility.

Having gone through the success story of the LNG-IUS in AUB through a span of almost four decades, where evidence-based recommendations have been made by gynaecologists all over the world, it is surely time to consider this device as a one-stop answer to AUB.

Compliance with Ethical Standards

Conflict of interest None of the authors have any conflict of interest in this article.

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