

Levonorgestrel intrauterine system: A first line medical therapy for idiopathic heavy menstrual bleeding

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ABSTRACT

Heavy menstrual bleeding or menorrhagia is a common menstrual disorder. Currently, both medical and surgical treatment options are available for the management of heavy menstrual bleeding. Hysterectomy, one of the surgical treatment options is associated with risks and is a costly procedure. Medical treatment may be preferred for the management of heavy menstrual bleeding. Oral medical treatments have various limitations for their use. For instance, cost is a limiting factor for tranexamic acid. Limited data is available to support the effectiveness of oral contraceptives. Poor patient compliance and intolerable adverse events are some other limitations especially in long term use. Levonorgestrel intrauterine system (LNG-IUS) is one of the common medical modalities in the management of heavy menstrual bleeding. LNG-IUS has been compared with other medical options like tranexamic acid, mefenamic acid, combined estrogen-progestogen, or progesterone alone, cyclic oral medroxyprogesterone acetate (MPA) oral norethisterone and low-dose combined oral contraceptive. LNG-IUS is more effective than usual medical treatment and also reduces the effect of heavy menstrual bleeding on quality of life. Similarly, it has shown similar therapeutic effects compared to endometrial ablation. Based on its efficacy, convenience and cost of therapy, it can be considered as the first line medical therapy for the management of heavy menstrual bleeding.

Keywords: Efficacy, Levonorgestrel, Menorrhagia

INTRODUCTION

Heavy menstrual bleeding/menorrhagia, a menstrual disorder with menstrual periods lasting more than seven days and/or blood loss > 80 ml is a common gynecological problem encountered in clinical practice.^{1,2} It affects about 24% women in the age groups of 36-40 years.¹ The causes of heavy menstrual bleeding may be

broadly divided into structural and non-structural. According to International Federation of Gynecology and Obstetrics (FIGO) classification system, the structural causes of abnormal uterine bleeding are grouped under "PALM" (polyp; adenomyosis; leiomyoma; malignancy and hyperplasia) while the non-structural causes are summarized as "COEIN" (coagulopathy; ovulatory dysfunction; endometrial; iatrogenic; and not yet classified) (Figure 1).³

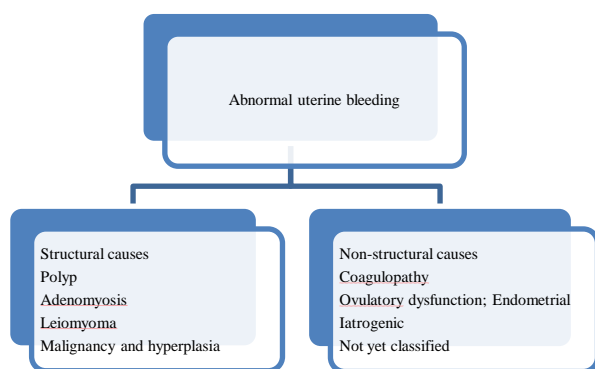


Figure 1: Causes of abnormal uterine bleeding

Untreated heavy menstrual bleeding may cause serious consequences in addition to adversely impacting the daily activities of women. Heavy menstrual bleeding may exacerbate or cause anemia and may be life threatening, at times if left untreated.⁴ Excessive menstrual bleeding may add up to the severity of anemia because of nutritional deficiency and parasitic infections in a country like India.⁵ The management of heavy menstrual bleeding poses many challenges to the treating physician.

Currently, available options for treating heavy menstrual bleeding may be broadly divided into medical and surgical modalities. The options for medical management include non-steroidal anti-inflammatory agents, tranexamic acid, combined hormonal contraceptives, cyclic progestins, danazol, and levonorgestrel-releasing intrauterine system (LNG-IUS) while the surgical treatment options are endometrial ablation / resection or hysterectomy.⁶

Hysterectomy may be a cure for excessive menstrual bleeding, but it is a major surgery associated with risks and is expensive. Endometrial ablation/ resection are procedures with their own complications, hence medical management may be preferred over surgical treatment.⁶

Oral medical treatments have various limitations for their use. For instance, cost is a limiting factor for tranexamic acid. Non-steroidal anti-inflammatory drugs (NSAIDs) though cheaper are not always effective.⁷ Concerns of the unacceptable adverse events limits the long term use of oral agents such as NSAIDs or contraceptives.⁸

An alternative to oral long term treatment is the use of intrauterine device. Levonorgestrel-releasing intrauterine system (LNG-IUS) is one of the commonly used medical treatments for heavy menstrual bleeding. Originally, LNG-IUS (trade name Mirena) was developed as contraceptive device.⁹ With time the use of LNG-IUS has also been studied in heavy menstrual bleeding associated with different gynecological conditions including uterine fibroids, endometriosis, adenomyosis and endometrial hyperplasia.¹⁰ The LNG-IUS has been approved in more than 100 countries for the treatment of menorrhagia/heavy menstrual bleeding.¹¹

LNG-IUS acts on the endometrium by releasing levonorgestrel. The local high concentration of LNG causes uniform suppression of endometrial proliferation resulting in reduction of menstrual blood loss and pain.²

Efficacy of levonorgestrel intrauterine system:

Numerous clinical trials have evaluated the efficacy and safety of LNG-IUS in reducing menstrual blood loss. In 2001, Stewart et al conducted a systemic review which included ten studies (five controlled trials and five case series). The objective of the review was to evaluate the effectiveness of 20 mcg levonorgestrel-releasing intrauterine system in menorrhagia. Out of ten studies, nine demonstrated statistically significant average menstrual blood loss reduction (ranging between 74-97%) with LNG-IUS. The LNG-IUS was found to be more effective than tranexamic acid.⁹

In a comparative study, Irvine et al (1998), reported that LNG-IUS was effective in reducing menstrual blood loss by 94% compared to 87% by oral norethisterone. The patient satisfaction rate with LNG-IUS was higher compared to oral norethisterone.¹²

In a pilot, non-comparative study, Montereio I et al (2002) evaluated the efficacy and performance of an intrauterine system releasing levonorgestrel (LNG-IUS, Mirena) 20 microgm/day for up to one year in the treatment of 44 adult women with menorrhagia.¹³ These patients were inserted LNG-IUS after the failure of other medical therapies. After insertion of LNG-IUS, there was significant improvement in hemoglobin levels at three and 12 months. About 80% of women continued the use of LNG-IUS beyond one year, thus proving that LNG-IUS was an effective treatment in women with menorrhagia.

Various other studies have compared LNG-IUS with the usual medical treatments (tranexamic acid, mefenamic acid, combined estrogen-progesterone, or progesterone alone), cyclic oral medroxyprogesterone acetate (MPA), oral norethisterone and low-dose combined oral contraceptive.^{12,14-16}

Use of LNG-IUS in patients of menorrhagia has shown to result in higher hemoglobin and serum ferritin levels compared to oral MPA. At cycle six, percentage of women with improved bleeding was much higher with the LNG-IUS compared to oral MPA as assessed by both investigator (93.6% vs. 61.0%) as well as patients (93.6% vs. 67.1%).¹⁵

Sayed et al, in single center study have shown that LNG-IUS is more effective in reducing menstrual blood loss compared to combined oral contraceptive in fibroid-related menorrhagia.¹⁶ Local intrauterine levonorgestrel has also shown to reduce endometrial thickness during the first three months of use suggesting its potential use in the treatment of endometrial hyperplasia.¹⁷ A

prospective observational study in patients with heavy menstrual bleeding from eight countries in the Asia-Pacific region has confirmed that the efficacy of conventional medical therapies including combined oral contraceptives, oral progestins, and anti-fibrinolytics, either alone or in combination, is inferior to LNG-IUS.¹⁸

LNG-IUS was more effective than usual medical treatment in reducing the effect of heavy menstrual bleeding on quality of life.¹⁴

Systematic reviews have consistently shown that in idiopathic heavy menstrual bleeding, LNG-IUS is the most effective medical therapy.¹¹ The evidence has also consistently shown that on the parameters of overall efficacy, acceptance and patient satisfaction, LNG-IUS scores over other medical treatment in the management of heavy menstrual bleeding.

LNG-IUS comparison with surgical option:

LNG-IUS has been compared with surgical option i.e. endometrial ablation. A meta-analysis of six randomized clinical trials has shown similar therapeutic effects of levonorgestrel intrauterine system in the management of heavy menstrual bleeding compared to endometrial ablation. Both treatments were associated with similar reduction in menstrual blood loss after six month, one year and two years.⁸

Indian evidence of LNG-IUS:

Efficacy of LNG-IUS has been studied in many prospective and non-comparative clinical studies in Indian patients. The details of these studies are given in Table 1.^{5,19-24}

Gupta et al reported 97% reduction in menstrual blood loss with LNG-IUS, at the end of one year.²⁰

Anemia is very common in women suffering from heavy monthly bleeding. Reduction in the menstrual bleeding loss and rise in hemoglobin and serum ferritin levels while treating heavy menstrual bleeding is particularly relevant in developing countries.²⁵ Global evidence has shown that, in addition to long term reduction in menstrual blood loss, LNG IUS also results in increase in hemoglobin levels.^{25,26} Similar results have been seen in Indian studies. LNG-IUS has shown to raise hemoglobin level from 5.5-22% over one year period in Indian patients (Figure 2).^{5,20,21} The rise in hemoglobin may be related to prevention of blood because of LNG-IUS.

Kriplani et al in an Indian study demonstrated effectiveness of LNG-IUS in the medical management of menorrhagia.⁵ A total of 71 % patients continued use of LNG-IUS. Menorrhagia was cured in all patients after three years of LNG-IUS use.⁵ In another prospective

observational study, LNG-IUS has been shown to be a safe and effective option for women with menorrhagia due to benign lesions of the uterus in perimenopausal women.²³

Recently, Kriplani et al have evaluated efficacy of the LNG-IUS in reducing menstrual blood loss in menorrhagia associated with myoma and idiopathic menorrhagia in Indian women.²² LNG-IUS resulted in high and sustained reduction of menstrual blood loss in both groups (Figure 3).

Table 1: Indian studies with LNG-IUS.

Authors	Study design	n	Indication
Kumar Sushil et al (2005) ¹⁹	Prospective, non-comparative study	20	Menorrhagia due to non-malignant Causes
Gupta B et al (2006) ²⁰	Comparative study of LNG-IUS and transcervical resection of the endometrium	50	Dysfunctional uterine bleeding
Kriplani A et al (2007) ⁵	Prospective, open, nonrandomized study	63	Menorrhagia but without uterine enlargement, endometrial hyperplasia with atypia, or endometrial carcinoma
Chattopdhyay B et al (2011) ²¹	Prospective, non-randomized study	42	Idiopathic menorrhagia with or without irregular cycle
Kriplani A et al (2012) ²²	Prospective comparative study	104	Myoma-related menorrhagia and idiopathic menorrhagia
Desai RM (2012) ²³	Prospective observational study	40	Menorrhagia due to benign lesions of the uterus
Mansukhani N et al (2013) ²⁴	Multicentric, retrospective, observational study	80	Abnormal uterine bleeding

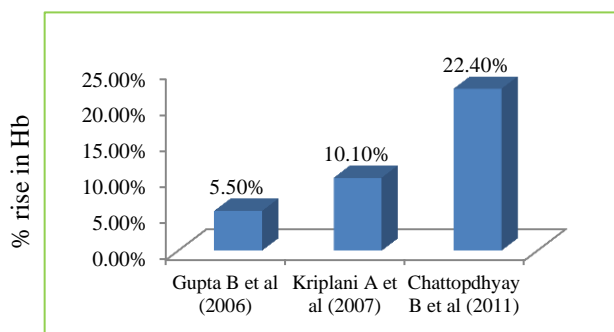


Figure 2: Increase in hemoglobin with LNG-IUS.

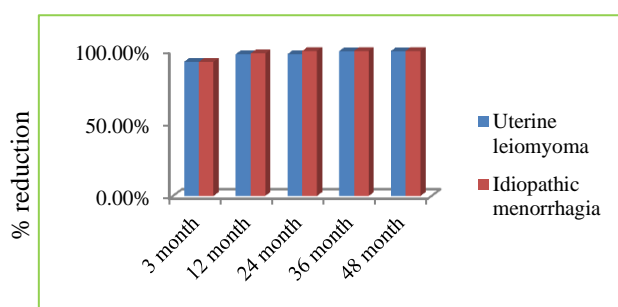


Figure 3: Sustained reduction in menstrual blood loss with LNG-IUS.

In an Indian study Kriplani et al have shown significant reduction in endometrial thickness by 3.4 mm at 12 months.⁷ In only study which compared surgical treatment with LNG-IUS, Gupta et al (2006) have shown that LNG-IUS is equally effective to transcervical resection of the endometrium (TCRE) in the treatment of dysfunctional uterine bleeding. However, LNG-IUS has an advantage of need of less operator skill and no operative risks.²⁰

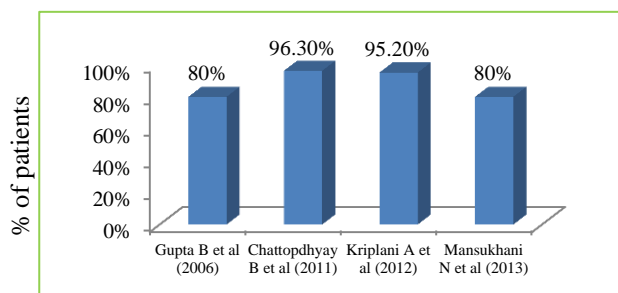


Figure 4: Patient satisfaction rates with LNG-IUS.

Safety of LNG-IUS is well established in Indian women. Premature removal of LNG-IUS has been reported in 0-14.8% patients while spontaneous expulsion has been reported in 2.38-9.5% patients.^{5,19,21} The common adverse events reported with LNG-IUS are intermenstrual spotting, amenorrhoea and oligomenorrhoea.^{5,19,21} Use of LNG-IUS is associated with high patient satisfaction (Figure 4). A multicentric, retrospective, review of patients with abnormal uterine bleeding (AUB) from

Pune, Delhi, and Gurgaon has showed overall 80% patient satisfaction.²⁴

Kriplani et al defined patient satisfaction as patients without premature removal of the LNG-IUS. Out of 104 patients, only five patients required premature removal of LNG-IUS, indicating patient satisfaction in about 95% of patients. Overall, Indian studies with LNG-IUS, have consistently shown high satisfaction rates ranging from 80-96%.^{5,20,21,24} Though there is no data on the efficacy and safety of LNG-IUS versus, other medical therapy, the results from Asia-Pacific study has shown superiority of LNG-IUS over conventional medical treatment. The most common reasons for discontinuation of LNG-IUS were adverse event or either bleeding.¹⁸ Overall, LNG-IUS has shown to be significantly effective, safe and convenient with no operative risks for the management of heavy menstrual bleeding in Indian patients.

Place for the use of LNG-IUS in idiopathic abnormal uterine bleeding

Medical therapy is the first line treatment for idiopathic abnormal uterine bleeding. According to the clinical practice guidelines (2010) on menorrhagia in idiopathic AUB, levonorgestrel intrauterine device (IUD) ranks the first in terms of efficacy. It scores over tranexamic acid, oral contraceptives as well as NSAIDs. The guidelines also recommend the placement of a levonorgestrel IUD for women with idiopathic abnormal uterine bleeding.¹

Similarly, authors of a recent systemic review on non-surgical management of heavy menstrual bleeding recommend the use of the levonorgestrel intrauterine system over oral contraceptive pills (OCPs), luteal-phase progestins, and NSAIDs for the reduction of blood loss in women with heavy menstrual bleeding.²⁷ Based on the compelling evidence of overall efficacy and safety from numerous clinical trials, use of LNG-IUS can be considered as the first line therapy for Indian patients with heavy menstrual bleeding (Figure 5).

Pre and post insertion clinical considerations for LNG-IUS

For improving the acceptance and satisfaction rate, thorough pre-insertion counselling should be done. The patients should be informed about all the possible associated side effects and potential benefits with insertion of LNG-IUS. The patients should also be emphasized that, if required, LNG-IUS can be removed any time. After the consent for insertion of LNG-IUS from patient, pelvic examination should be performed so as to understand the size, shape and mobility of the uterus. The LNG-IUS should be inserted as per the recommendations in the package insert. After the insertion, patients should be demonstrated how to feel the thread and report in case, they are not been able to feel it.

During follow-up visits, the placement of LNG IUS should be checked with clinical examination and visualization of threads. If LNG-IUS is not seen in place and can-not be visualized during examination, ultrasound should be ordered to rule out its expulsion or perforation. Locating LNG-IUD on ultrasound may be more difficult compared to copper containing devices because of

different ultrasound appearance because of non-uniform hyperechogenic nature of the device.²⁸ If ultrasound is unable to detect device, then X ray of abdomen should be performed to see, if it has been placed outside the uterus. X ray is an easy and economical modality of investigation to detect location of LNG-IUS outside the uterus.²

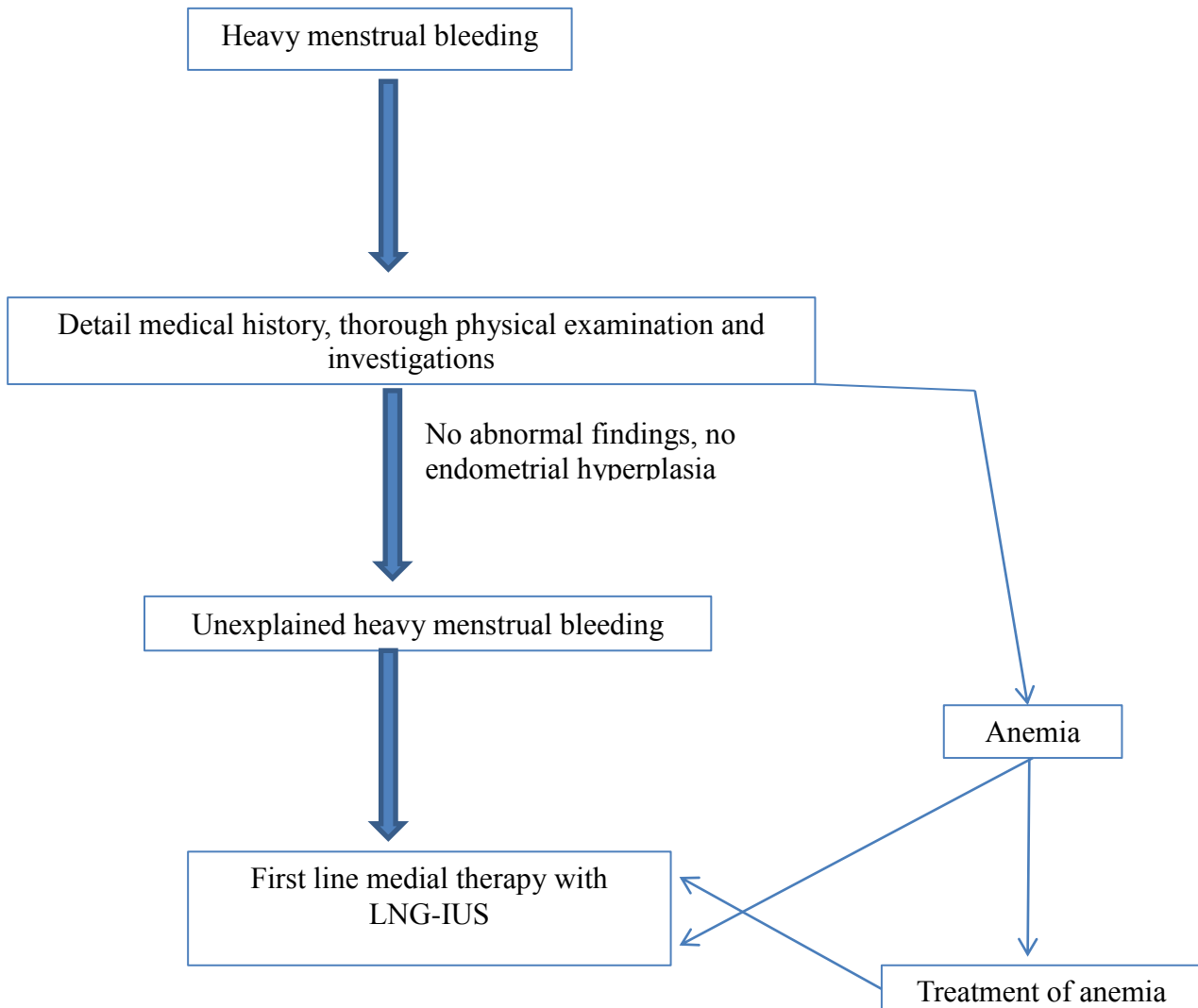


Figure 5: Proposed flow chart for use of LNG-IUS.

CONCLUSION

Heavy menstrual bleeding is a common gynecological problem. In most of the patients with idiopathic heavy menstrual bleeding, no pelvic pathology is seen. In such patients, medical therapy should be the first line treatment. LNG-IUS can be considered as first line medical therapy, based on the evidence of its effectiveness in reducing blood loss, improvement in hemoglobin level, patient satisfaction and no operative risk.

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REFERENCES

1. Marret H, Fauconnier A, Chabbert-Buffet N, Cravello L, Golfier F, Gondry J, et al. Clinical practice guidelines on menorrhagia: management of

- abnormal uterine bleeding before menopause. *Eur J Obstet Gynecol Reprod Biol.* 2010;152:2:133-7.
2. 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;4:8-15.
 3. Munro MG, Critchley HOD, Broder MS, Fraser IS. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. *International Journal of Gynecology and Obstetrics.* 2011;113:3-13.
 4. Harlow SD, Campbell OMR. Epidemiology of menstrual disorders in developing countries: a systematic review *BJOG: an International Journal of Obstetrics and Gynaecology.* 2004;111:6-16.
 5. Kriplani A, Singh BM, Lal S, Agarwal N. Efficacy, acceptability and side effects of the levonorgestrel intrauterine system for menorrhagia. *International Journal of Gynecology and Obstetrics.* 2007;97:190-4.
 6. Grimes DA. Review of management strategies for heavy menstrual bleeding: Summary of the best evidence. Supplement to *OBG Management.* 2009;S7-S10.
 7. Sweet MG, Schmidt-Dalton TA, Weiss PM, Madsen KP. Evaluation and Management of Abnormal Uterine Bleeding in Premenopausal Women. *Am Fam Physician.* 2012;85:35-43.
 8. Kaunitz AM, Meredith S, Inki P, Kubba A, Sanchez-Ramos L. Levonorgestrel-releasing intrauterine system and endometrial ablation in heavy menstrual bleeding: a systematic review and meta-analysis. *Obstet Gynecol.* 2009;113:1104-16.
 9. Stewart A, Cummins C, Gold L, Jordan R, Phillips W. The effectiveness of the levonorgestrel-releasing intrauterine system in menorrhagia: a systematic review. *British Journal of Obstetrics and Gynaecology.* 2001;108:74-86.
 10. Heikinheimo O, Gemzell-Danielsson K. Emerging indications for the levonorgestrel-releasing intrauterine system (LNG-IUS). *Acta Obstetrica et Gynecologica Scandinavica.* 2012; 91:3-9.
 11. Nelson AL. LNG-IUS: First-line therapy for idiopathic heavy menstrual bleeding. *The Female Patient.* 2010;3:39-43.
 12. Irvine GA, Campbell-Brown MB, Lumsden MA, Heikkilä A, Walker JJ, Cameron IT. Randomised comparative trial of the levonorgestrel intrauterine system and norethisterone for treatment of idiopathic menorrhagia. *Br J Obstet Gynaecol.* 1998;105:592-8.
 13. Monterio 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;65:325-8.
 14. Gupta J, Kai J, Middleton L, Pattison H, Gray R, Daniels J et al. Levonorgestrel intrauterine system versus medical therapy for menorrhagia. *N Engl J Med.* 2013;368:128-37.
 15. Kaunitz AM, Bissonnette F, Monteiro I, Lukkari-Lax E, DeSanctis Y, Jensen J. Levonorgestrel-releasing intrauterine system for heavy menstrual bleeding improves hemoglobin and ferritin levels. *Contraception.* 2012;86:452-7.
 16. Sayed GH, Zakherah MS, El-Nashar SA, Shaaban MM. A randomized clinical trial of a levonorgestrel-releasing intrauterine system and a low-dose combined oral contraceptive for fibroid-related menorrhagia. *Int J Gynaecol Obstet.* 2011;112:126-30.
 17. Pakarinen P, Luukkainen T, Laine H, Lahteenmaki P. The effect of local intrauterine levonorgestrel administration on endometrial thickness and uterine blood circulation. *Hum Reprod.* 1995;10:2390-4.
 18. Lee BS, Lin X, Asif S, Kraemer P, Hanisch JU, Inki P. Levonorgestrel-releasing intrauterine system versus conventional medical therapy for heavy menstrual bleeding in the Asia-Pacific region. *Int J Gynecol Obstet,* 2013.
 19. Kumar Sushil , Antony ZK, Mohindra V, Kapur A. Therapeutic use of LNG intrauterine system (Mirena) for menorrhagia due to benign lesions – An alternative to hysterectomy? *J Obstet Gynecol.* 2005;6:541-3.
 20. Gupta B, Mittal S, Misra R, Deka D, Dadhwal V. Levonorgestrel-releasing intrauterine system vs. transcervical endometrial resection for dysfunctional uterine bleeding. *Int J Gynaecol Obstet.* 2006;95:26106.
 21. Chattopdhyay B, Nigam A, Goswami S, Chakravarty PS. Clinical outcome of Levonorgestrel Intra-Uterine system in idiopathic menorrhagia. *European Review for Medical and Pharmacological Sciences.* 2011;15:764-8.
 22. Kriplani A, Awasthi D, Kulshrestha V, Agarwal N. Efficacy of the levonorgestrel-releasing intrauterine system in uterine leiomyoma. *International Journal of Gynecology and Obstetrics.* 2012;116:35-8.
 23. Desai RM. Efficacy of levonorgestrel releasing intrauterine system for the treatment of menorrhagia due to benign uterine lesions in perimenopausal women. *J Midlife Health.* 2012;3:20-3.
 24. Mansukhani N, Unni J, Dua M, Darbari R, Malik S, Verma S et al. Are women satisfied when using levonorgestrel-releasing intrauterine system for treatment of abnormal uterine bleeding? *J Midlife Health.* 2013;4:31-5.
 25. Xiao B, Wu S-C, Chong J, Zeng T, Han L-H, Luukkainen T. Therapeutic effects of the levonorgestrel releasing intrauterine system in the treatment of idiopathic menorrhagia. *Fertility and Sterility.* 2003;79:963-9.
 26. Endrikat J, Vilos G, Muysers C, Fortier M, Solomayer E, Lukkari-Lax E. The levonorgestrel-releasing intrauterine system provides a reliable, long-term treatment option for women with idiopathic menorrhagia. *Arch Gynecol Obstet.* 2012;285:117-21.
 27. Matteson KA, Rahn DD, Wheeler TL, Casiano E, Siddiqui NY, Harvie HS et al. Nonsurgical

- management of heavy menstrual bleeding- A systematic review. *Obstet Gynecol.* 2013;0:1–12.
28. Gowri V, Mathew M. Ultrasound Location of Misplaced Levonorgestrel Releasing Intrauterine System (LNG-IUS) – is it easy? *Oman Med J.* 2009;24:54–5.
29. Shambhu S, Pappas M. The “lost” Mirena: What investigations are required ? An intraperitoneal levonorgestrel-releasing intrauterine system following uterine perforation: Case report. *BMJP.* 2009;2:38-40.

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