

Abnormal uterine bleeding in midlife: The role of levonorgestrel intrauterine system

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ABSTRACT

Abnormal uterine bleeding is a common gynecological complaint affecting 10-30% of women in midlife and constitute about one-third of all outpatient gynecological visits. It adversely affects the quality of woman's life and can lead to psychological, social, medical, and sexual problems and thus necessitating appropriate and adequate management. Different treatment modalities for such problems are available, yet the levonorgestrel intrauterine system (LNG-IUS) has recently provided a good treatment option effective in treating such complaints and at the same time, having a reliable contraceptive effect which is desired by such age group. For women in their reproductive years, the LNG-IUS has become one of the most acceptable medical treatments for menorrhagia, reducing referrals to specialists, and decreasing the recourse to operative treatments. It is easy to insert, has a sustained effect, cost-effective, and well tolerated besides providing reliable contraception.

Key Words: Abnormal uterine bleeding, fibroids, hysterectomy, levonorgestrel intrauterine system, menorrhagia, mirena, uterus

INTRODUCTION

Abnormal uterine bleeding (AUB), defined as a change in any or a combination of frequency, duration, or amount of bleeding, is a common gynecological complaint that affects 10-30% of reproductive-aged women and constitute about one-third of all outpatient gynecological visits.^[1] The abnormal bleeding patterns can be annoying and adversely affect the quality of woman's life since unpredictable or heavy bleeding can lead to psychological, social, medical, and sexual problems and thus necessitate appropriate and adequate management.

Apart from bleeding related to pregnancy, menorrhagia in reproductive-aged women can result from different causes including dysfunctional uterine bleeding (DUB), organic lesions as fibroids, adenomyosis as well as systemic causes such as coagulopathies (e.g., Von Willebrand's disease or use of anticoagulants). Different treatment modalities for such problem are available, yet the levonorgestrel intrauterine system (LNG-IUS) has recently provided a good treatment option effective in treating such complaint

and at the same time, having a reliable contraceptive effect which is desired by such age group. We aim to highlight the role of LNG-IUS in the treatment of AUB in reproductive-aged women.

THE LEVONORGESTREL-INTRAUTERINE SYSTEM

The LNG-IUS, which is marketed under the name of Mirena (Bayer Health Care Pharmaceuticals Inc, Wayne, NJ), is similar in shape to the Cu-T intrauterine device with the vertical stem containing a mixture of 52 mg of levonorgestrel and polydimethylsiloxane (PMDS) surrounded by rate-controlling PDMS capsule. It is impregnated with barium sulfate rendering the device radiopaque. Figure 1 shows hysteroscopic view of LNG-IUS properly placed inside the uterus. The LNG-IUS allows a steady local release of 20 ug of levonorgestrel per day. The intrauterine concentrations

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Figure 1: Hysteroscopic view of LNG-IUS inside the uterine cavity

of levonorgestrel released by intrauterine system have been estimated to be 1000 times higher than that with a levonorgestrel subdermal implant.^[2] This high level of levonorgestrel in the endometrium induces dramatic effects leading to the unique mode of contraceptive and therapeutic action of the LNG-IUS. Initially developed to decrease the risk of expulsion of the intrauterine contraceptive device by reducing myometrial contractility, LNG-IUS has been found to result in dramatic reduction in the menstrual blood loss which led researchers to investigate its role as an alternative to surgery for the treatment of AUB especially in reproductive-aged women.

LEVONORGESTREL INTRAUTERINE SYSTEM FOR THE TREATMENT OF DYSFUNCTIONAL UTERINE BLEEDING

The use of LNG-IUS was found to reduce menstrual blood flow which subsequently led to rise in the serum ferritin levels and hemoglobin levels in women with normal menstrual blood loss as well as in those with heavy menstruation.^[3] It was found to reduce blood loss by 86% after 3 months of use and up to 97% by 12 months of use.^[4] More recent evidence shows that in women with heavy menstrual blood loss, the LNG-IUS can normalize blood flow, with up to 35% of women being amenorrheic at 24 months. Several studies have compared the efficacy of LNG-IUS in treating menorrhagia with other treatment modalities.

Levonorgestrel intrauterine system versus medical treatment

Women with menorrhagia treated with LNG-IUS were found to have more reduction in the menstrual blood flow than those who used non-steroidal anti-inflammatory drugs or anti-fibrinolytic agents (tranexamic acid).^[5] Moreover, when compared to norethisterone 5 mg (three

times a day from day 5 to day 26 of the cycle) in a three cycle randomized study, LNG-IUS was found to be more effective in reducing menstrual blood flow (94% in the LNG-IUS group and 87% in the oral norethisterone group). In the same study, only 22% of women wished to continue treatment in the norethisterone arm compared to 76% of women using the LNG-IUS.^[6]

Levonorgestrel intrauterine system versus surgical treatment

Hysterectomy has long been the definitive treatment for refractory cases with DUB who failed to respond to medical treatment. However, since the late 1990s, evidence started accumulating to suggest that the LNG-IUS can be a safe and effective medical alternative to hysterectomy. This was proved in two studies which documented that 64-82% of patients who had the LNG-IUS inserted for temporary control of their AUB, pending hysterectomy declined proceeding with the hysterectomy.^[7,8]

LNG-IUS was found to be almost equally as effective as endometrial ablation or resection which emerged as a new minimally invasive procedure for the treatment of menorrhagia. This was proved in the study by Crosignani *et al.*, who randomized women to either an endometrial resection or LNG-IUS to control their heavy menstrual bleeding.^[9] This study demonstrated a reduction in the pictorial blood loss assessment chart (PBAC) at 12 months by 79% in the LNG-IUS users and 89% in those women who had undergone a resection. Amenorrhea or infrequent bleeding was reported by 65% of women using the LNG-IUS compared with 71% who underwent a resection. Satisfaction was high in both groups, with no significant difference in health-related quality-of-life scores.^[9]

A Cochrane systematic review appraised the literature and concluded that surgery, especially hysterectomy, reduces menstrual bleeding at 1 year more than medical treatments but LNG-IUS appears equally effective in improving quality of life. The evidence for longer-term comparisons is weak and inconsistent.^[10]

Levonorgestrel intrauterine system and menorrhagia due to bleeding disorders

It is estimated that about 13% of women with menorrhagia suffer from von Willebrand's disease.^[11] When the effect of the LNG-IUS on hemostasis in women with menorrhagia was studied, it showed high expression of fibrinolytic inhibitors (plasminogen activator inhibitor 1 and 2) and up-regulated urokinase-type plasminogen activator receptor expression in the endometrium.^[12] This may explain why the LNG-IUS successfully treated heavy menstrual blood loss in cases with inherited

bleeding disorders.^[13] LNG-IUS is effective in reducing the duration and amount of menstrual bleeding in women with menorrhagia associated with the use of oral anticoagulation.^[14]

WHAT ABOUT MENORRHAGIA DUE TO PATHOLOGICAL UTERINE LESIONS?

Results from trials of the LNG-IUS to treat leiomyoma-related menorrhagia are conflicting. Although Grigorieva *et al.*,^[15] reported reduced blood loss and improved hematocrits in these women, Mercorio *et al.*,^[16] did not confirm these findings. The effect may depend on the initial fibroid size and position. There is some evidence that expulsion rates may be increased in the presence of submucous fibroids.^[17] Recently, Kriplani *et al.* reported that use of the LNG-IUS appears to lead to a significant reduction in the uterine volume of women with menorrhagia, as well as reducing the MBL in women with uterine leiomyomas.^[18] Women with adenomyosis-related menorrhagia may benefit as well from the use of LNG-IUS with normalization of their menstrual flow.^[19] It may also be a useful adjuvant therapy following endometrial resection to help adenomyosis-related menorrhagia. Gonadotropin releasing hormone agonists (GnRH-a) also are one of the effective methods to decrease the menstrual blood loss in patients with DUB or AUB due to pathological uterine lesions,^[20] but their side effects prevent their long term use. However, LNG-IUS has been shown to have comparable results, and also comparable clinical efficacy to GnRH analogues or progestins for the symptomatic treatment of endometriosis.^[21]

CONCLUSION

For women in their reproductive years, the LNG-IUS has become one of the most acceptable medical treatments for menorrhagia, reducing referrals to specialists, and decreasing the recourse to operative treatments. It is easy to insert, has a sustained effect, cost-effective, and well tolerated besides providing reliable contraception. In a recent risk-benefit review,^[22] it has been brought out that LNG-IUS has a positive effect on most quality-of-life domains, comparable to those achieved with hysterectomy or endometrial ablation, and is consistently a cost-effective option across a variety of countries and settings. It concluded that LNG-IUS is an effective treatment option for women with heavy menstrual bleeding, including those with underlying organic pathology or bleeding disorders. As has been brought out that LNG-IUS appears equally effective as hysterectomy in improving quality of life in patients of DUB, it can serve to bring down the incidence of hysterectomies. Mirena can help us save the uterus!

REFERENCES

1. Cooper JM. Contemporary management of abnormal uterine bleeding. Preface. *Obstet Gynecol Clin North Am* 2000;27:11-3.
2. Nilsson CG, Haukkamaa M, Vierola H, Luukkainen T. Tissue concentrations of levonorgestrel in women using a levonorgestrel-releasing IUD. *Clin Endocrinol (Oxf)* 1982;17:529-36.
3. Xiao B, Wu SC, Chong J, Zeng T, Han LH, Luukkainen T. Therapeutic effects of the levonorgestrel-releasing intrauterine system in the treatment of idiopathic menorrhagia. *Fertil Steril* 2003;79:963-9.
4. Andersson JK, Rybo G. Levonorgestrel-releasing intrauterine device in the treatment of menorrhagia. *Br J Obstet Gynaecol* 1990;97:690-4.
5. Milsom I, Andersson K, Andersch B, Rybo G. A comparison of flurbiprofen, tranexamic acid, and a levonorgestrel-releasing intrauterine contraceptive device in the treatment of idiopathic menorrhagia. *Am J Obstet Gynecol* 1991;164:879-83.
6. 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.
7. Barrington JW, Bowen-Simpkins P. The levonorgestrel intrauterine system in the management of menorrhagia. *Br J Obstet Gynaecol* 1997;104:614-6.
8. Lähteenmäki P, Haukkamaa M, Puolakka J, Riikonen U, Sainio S, Suvisaari J, *et al.* Open randomised study of use of levonorgestrel releasing intrauterine system as alternative to hysterectomy. *BMJ* 1998;316:1122-6.
9. Crosignani PG, Vercellini P, Mosconi P, Oldani S, Cortesi I, De Giorgi O. Levonorgestrel-releasing intrauterine device versus hysteroscopic endometrial resection in the treatment of dysfunctional uterine bleeding. *Obstet Gynecol* 1997;90:257-63.
10. Marjoribanks J, Lethaby A, Farquhar C. Surgery versus medical therapy for heavy menstrual bleeding. *Cochrane Database Syst Rev* 2003;2:CD003855.
11. Tam WH, Yuen PM, Shan Ng DP, Leung PL, Lok IH, Rogers MS. Health status function after treatment with thermal balloon endometrial ablation and levonorgestrel intrauterine system for idiopathic menorrhagia: A randomized study. *Gynecol Obstet Invest* 2006;62:84-8.
12. Koh SC, Singh K. The effect of levonorgestrel-releasing intrauterine system use on menstrual blood loss and the hemostatic, fibrinolytic/inhibitor systems in women with menorrhagia. *J Thromb Haemost* 2007;5:133-8.
13. Kingman CE, Kadir RA, Lee CA, Economides DL. The use of levonorgestrel-releasing intrauterine system for treatment of menorrhagia in women with inherited bleeding disorders. *BJOG* 2004;111:1425-8.
14. Pisoni CN, Cuadrado MJ, Khamashta MA, Hunt BJ. Treatment of menorrhagia associated with oral anticoagulation: Efficacy and safety of the levonorgestrel releasing intrauterine device (Mirena coil). *Lupus* 2006;15:877-80.
15. Grigorieva V, Chen-Mok M, Tarasova M, Mikhailov A. Use of a levonorgestrel-releasing intrauterine system to treat bleeding related to uterine leiomyomas. *Fertil Steril* 2003;79:1194-8.
16. Mercorio F, De Simone R, Di Spiezio Sardo A, Cerrota G, Bifulco G, Vanacore F, *et al.* The effect of a levonorgestrel-releasing intrauterine device in the treatment of myoma-related menorrhagia. *Contraception* 2003;67:277-80.
17. Ikomi A, Pepra EF. Efficacy of the levonorgestrel intrauterine system in treating menorrhagia: Actualities and ambiguities.

- J Fam Plann Reprod Health Care 2002;28:99-100.
18. Awasthi D, Kulshrestha V, Agarwal N. Efficacy of the levonorgestrel-releasing intrauterine system in uterine leiomyoma. *Int J Gynaecol Obstet* 2012;116:35-8.
19. Fedele L, Bianchi S, Raffaelli R, Portuese A, Dorta M. Treatment of adenomyosis-associated menorrhagia with a levonorgestrel-releasing intrauterine device. *Fertil Steril* 1997;68:426-9.
20. Magon N. Gonadotropin releasing hormone agonists: Expanding vistas. *Indian J Endocr Metab* 2011;15:261-7.
21. Heikinheimo O, Gemzell-Danielsson K. Emerging indications for the levonorgestrel-releasing intrauterine system. *Acta Obstet Gynecol Scand* 2012;91:3-9.
22. Kaunitz AM, Inki P. The levonorgestrel-releasing intrauterine system in heavy menstrual bleeding: A benefit-risk review. *Drugs* 2012;72:193-215.

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