

Clinical applications of levonorgestrel-releasing intrauterine system to gynecologic diseases

Mi-La Kim, Seok Ju Seong

Department of Obstetrics and Gynecology, CHA Gangnam Medical Center, CHA University, Seoul, Korea

The levonorgestrel-releasing intrauterine system (LNG-IUS), originally designed for contraception, has since been applied to various gynecologic diseases. This article summarizes the current status of clinical applications of LNG-IUS to the treatment of gynecologic diseases such as heavy menstrual bleeding, endometriosis, leiomyoma, adenomyosis, endometrial hyperplasia, and early-stage endometrial cancer.

Keywords: Adenomyosis; Endometrial cancer; Endometrial hyperplasia; Endometriosis; Leiomyoma; Levonorgestrel-releasing intrauterine system; Menorrhagia

Introduction

The levonorgestrel-releasing intrauterine system (LNG-IUS), designed initially in the mid-1970s, provides highly effective, safe, and long-term reversible contraception. More than 120 countries, including Korea, have approved it for use [1]. The approved Korean applications include contraception, treatment of heavy menstrual bleeding, treatment of dysmenorrhea, and endometrial protection during estrogen replacement therapy in postmenopausal women. LNG-IUS is a T-shaped device that releases 20 µg/day of LNG into the uterine cavity over a 5-year period [2]. LNG-IUS provides, by contrast with the relatively low serum levels, locally high concentrations of LNG in the endometrium and adjacent tissues. This leads to decidualization of the stroma, mucosal thinning, and eventually, by suppression of endometrial growth, an inactive endometrium [3]. It has been demonstrated that LNG-IUS, additionally to its high contraceptive efficacy, benefits women also in the treatment of gynecologic diseases related to heavy menstrual bleeding and dysmenorrhea, which include endometriosis, leiomyoma, adenomyosis, endometrial hyperplasia, and early-stage endometrial cancer [4,5]. In this article, we summarize the current clinical applications status of LNG-IUS as relates to gynecologic diseases.

Heavy Menstrual Bleeding

Heavy menstrual bleeding (HMB), clinically defined as greater

than 80 mL of blood loss per menstrual cycle, is a common health problem in women. Hysterectomy is an often-employed treatment option, though various alternative approaches, such as tranexamic acid, nonsteroidal anti-inflammatory drugs, danazol, combined oral pills, progestins, and LNG-IUS, also can be successful.

Hurskainen et al. [6] conducted a 5-year randomized comparison of clinical outcomes and costs associated with the use of LNG-IUS and hysterectomy for treatment of HMB. In the results, patient' satisfaction and quality of life were similar, but costs were 40% lower in the LNG-IUS group. Lethaby et al. [7] published a review of ten randomized controlled trials with reproductive-aged women treated with LNG-IUS versus medical (cyclic progestins) or surgical therapy (hysteroscopic endometrial resection, thermal ablation, or hysterectomy). LNG-IUS

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Corresponding author: Seok Ju Seong

Department of Obstetrics and Gynecology, CHA Gangnam Medical Center, CHA University, 566 Nonhyeon-ro, Gangnam-gu, Seoul 135-081, Korea

Tel: +82-2-3468-3673 Fax: +82-2-558-1112

E-mail: sjseongcheil@naver.com

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was more effective than cyclic progestins; and whereas side effects were more common, the LNG-IUS patients were more satisfied with their results. Endometrial ablation was more effective than LNG-IUS for reduction of menstrual blood loss, and yet there was no difference in patient' satisfaction between the groups. Once again, women treated with LNG-IUS experienced more drug-induced side effects, but there was no significant difference in their perceived quality of life. Comparing LNG-IUS with hysterectomy, the former was more cost effective, and there were no significant differences in the quality of life measures [7]. Gupta et al. [8] conducted a multicenter, randomized controlled trial involving 571 women with HMB who were treated with LNG-IUS or the usual medical therapy (tranexamic acid, mefenamic acid, combined estrogen-progestogen, or progestogen alone). In both groups, the patient-reported scores on the menorrhagia multi-attributes scale (MMAS) improved from the baseline to six months, though the LNG-IUS group showed significantly better improvement sustainment over a 2-year period ($P<0.001$). Moreover, all of the MMAS domains showed significantly superior improvements for the LNG-IUS group. Also, at 2 years, the LNG-IUS group had a higher continuation rate than the usual-medical-treatment group (64% vs. 38%, $P<0.001$), with no significant differences in the rates of hysterectomy, endometrial ablation or sexual activity scores [8]. The LNG-IUS is a good alternative to surgical management such as hysterectomy and endometrial ablation in heavy menstrual bleeding. In ESHRE Capri Workshop Group [9], they recommended that the LNG-IUS or other medical treatments firstly adopted in treatment of HMB. Overall, LNG-IUS was proved to be highly effective in reducing menstrual blood loss, was well tolerated, boasted a high user-satisfaction rate, and was cost effective [9]. Currently, LNG-IUS is considered to be the first-line treatment for HMB [10].

Endometriosis

Endometriosis is associated with dysmenorrhea, dyspareunia, non-cyclic pelvic pain, and subfertility. For women with dysmenorrhea, reported endometriosis incidences have been as high as 40% to 60% [11,12]. Endometriosis is a chronic disease that has a recurrence rate of approximately 10% to 15% one year after conservative surgical treatment alone, and fully 40% to 50% at 5 years' follow-up [13,14]. Cheong et al. [15], having conducted a retrospective study, reported re-operation

rate as high as 51% for a 10-year period. Recurrence is a important issue indeed, as repeated surgery can significantly impact upon the patient's quality of life and endanger her future fertility [16]. In order to prolong symptom-free interval and prevent recurrence, postoperative adjunctive hormonal therapy usually is prescribed. Gonadotropin releasing hormone (GnRH) agonist, danazol, combined oral contraceptives, and progestins are the common hormonal methods employed for the management of endometriosis-related pain. GnRH agonist is the gold standard for adjunctive treatment of endometriosis [17]. Such treatment often needs to be continued many years or until pregnancy is desired. Although effective, the hypoestrogenism induced by the GnRH agonist is associated with systemic side effects, which can affect patient' compliance and preclude long-term use. Thus, new therapeutic options, including the continuous use of oral pills or LNG-IUS, are being explored [18-21].

Several hypotheses have been formulated to explain the mechanism of action of LNG-IUS in endometriosis-related pain. One is a local effect on the ectopic endometrium resulting from depletion of the estrogen and progesterone receptors though inhibition of synthesis and expression of estrogen and progestin receptors [22,23]. Other possibilities are a direct effect on the eutopic endometrium by inhibition of endometrial production of estrogen-induced growth factors or growth factor-binding protein, as resulting in an anti-proliferative effect, glandular atrophy and decidualization [24]. Or, the LNG-IUS effect might be a function of a reduction of local vascular angiogenesis, a reduction in pelvic-vessel congestion and an increase in apoptosis, a reduction in peritoneal fluid macrophage activity and a modification in the production of cytokines responsible for maintenance of lesions and pain [25-28].

LNG-IUS was first used for endometriosis-related dysmenorrhea by Vercellini et al. [29]. They reported that it greatly reduced menstrual pain and was highly rated in terms of patient satisfaction. As a follow-up to this pilot study, Vercellini et al. [30] thoroughly investigated the application of LNG-IUS to endometriosis in a randomized controlled trial, comparing it with expectant management after laparoscopic conservative surgery. According to a post-12-month evaluation, and an intention-to-treat analysis, postoperative recurrence of dysmenorrhea was significantly decreased in the LNG-IUS group (10% vs. 45%, $P=0.03$). Tanmahasamut et al. [31], similarly, conducted a double-blind randomized controlled trial with 55 post-conservative-surgery patients. At 12 months, the LNG-

IUS group relative to an expectant group, showed a greater reduction in dysmenorrhea visual analogue scale (VAS) (-81 mm vs. -50 mm, $P=0.06$) and pelvic pain VAS (-48.5 mm vs. -22 mm, $P=0.038$). Recurrent dysmenorrhea within one year also was reduced in the LNG-IUS group (7.4% vs. 39.1%, $P=0.014$) [31]. Petta et al. [32] conducted a multicenter randomized controlled trial to compare LNG-IUS ($n=39$) with a GnRH agonist ($n=43$), finding no statistical differences in VAS pain score or quality-of-life improvement. However, Bayoglu et al. [33] reported different results for a 12-month prospective randomized study involving 40 severe endometriosis patients. They reported that the total endometriosis severity profile (TESP) score decreased in the LNG-IUS group over the initial 6 months, but that by 12 months of follow-up, the TESP scores had risen back to values similar to those at pretreatment. At the end of the study, the LNG-IUS group relative to the GnRH subjects showed a significant increase in VAS and TESP scores, and recorded lower levels of satisfaction [33]. Even so, given the additional advantages of LNG-IUS, namely the facts that it is not associated with hypoestrogenism and the possibility of long-term (5-year) use, it may yet be used for chronic pelvic pain-associated endometriosis in women who do not wish to conceive.

Leiomyoma

Leiomyoma is the most common benign gynecologic tumor in reproductive-aged women, producing symptoms including HMB, dysmenorrhea, pelvic pressure and pain, and reproductive dysfunction, though many patients remain asymptomatic [34,35].

In many studies, LNG-IUS use by leiomyoma patients ameliorated leiomyoma-related menorrhagia. This treatment modality is utilized primarily in cases of leiomyoma-related HMB, though treatment is not as effective as for idiopathic HMB [36-41]. Sivin and Stern [42] reported a multicenter prospective 7-year randomized study, the chief finding of which was that long-term use of LNG-IUS reduced the incidence of newly developed myoma and myoma-related surgery in comparison with copper T. However, there is no coherence to changes of uterine volume or leiomyoma volume in users of LNG-IUS [36,41,43].

There are some limitations on the suitability of LNG-IUS for women with leiomyoma, including leiomyomas causing

distortion of the uterine cavity or cases of submucosal myoma [44]. The reported LNG-IUS expulsion rates among women with uterine leiomyomas range between 0% and 20%, and are higher than those without uterine leiomyoma (0% to 3%). Also, significantly higher rates of expulsion have been noted among women with greater uterine volumes (a possible proxy for fibroid size) than among those with smaller ones [36-39,45,46].

Adenomyosis

Adenomyosis characterized by the presence of heterotopic endometrial glands and stroma in the myometrium, is a common cause of menorrhagia and dysmenorrhea. The definitive treatment is hysterectomy, at least traditionally. However, alternative management, including oral pills, danazol, GnRH agonist, LNG-IUS, endometrial ablation/resection, uterine artery embolization, and magnetic resonance guided focused ultrasound also can be considered [47-55].

The use of LNG-IUS for adenomyosis was first reported by Fedele et al. [50], in 1997. They evaluated the efficacy of LNG-IUS in 25 patients suffering from adenomyosis-associated menorrhagia, and found that 92% of them showed decreases on the pictorial blood loss assessment chart (PBAC) and diminished dysmenorrheal symptoms, along with significant increases in hemoglobin, hematocrit, and serum ferritin levels [50]. Bragheto et al. [56] reported on the employment of LNG-IUS in the treatment of 29 adenomyosis patients diagnosed and monitored by magnetic resonance imaging. After 6 months, significant reductions of junctional zone thickness and VAS pain scores were observed, though there was no significant change in uterine volume. Cho et al. [57] and Sheng et al. [58] reported 3-year follow-up data on the application of LNG-IUS for the treatment of adenomyosis, in which indicated significantly decreased menorrhagia and VAS pain scores and high patient' satisfaction. Additionally to these observational study, Ozdegirmenci et al. [59] compared LNG-IUS with hysterectomy in a prospective randomized trial, the results of which showed that the LNG-IUS group enjoyed significant and comparable improvements in hemoglobin levels and along with superior health-related quality of life improvements during the first year. Conclusively, LNG-IUS is an effective treatment option for management of dysmenorrhea and menorrhagia in patients with clinically diagnosed

adenomyosis. As such, it offers patients a practical alternative to hysterectomy.

Endometrial Hyperplasia

Endometrial hyperplasia is defined as a morphologic and biologic alteration of the endometrium as a result of continuous estrogenic stimulation unopposed by adequate levels of progesterone. Among reproductive-aged women, chronic anovulation, commonly seen in those diagnosed with polycystic ovarian syndrome, is the most common cause of endogenous unopposed estrogen [60].

Hormonal therapy is regarded as the standard management plan for endometrial hyperplasia without atypia or benign endometrial hyperplasia, owing to the facts that the malignancy potential is low, the spontaneous resolution rate is high, and the response to hormonal therapy, moreover, also is high [61,62]. In the case of atypical endometrial hyperplasia, total hysterectomy with or without bilateral salpingo-oophorectomy is the current standard treatment option [63]. However, hormonal therapy can be selected in atypical endometrial hyperplasia patients who desire to preserve their fertility or in patients who are poor surgical candidates due to severe medical comorbidities. The hormonal classes with potential therapeutic options include progestins, selective estrogen receptor modulators, aromatase inhibitors, and gonadotropin-releasing hormone agonists. Among these, progestin is most commonly used as the safe, uterus-preserving alternative to hysterectomy. Nonetheless, systemic side effects and poor compliance reportedly are associated with oral progesterone; clinical trials of progestin therapies for atypical endometrial hyperplasia, furthermore, have not yet established a standard regimen [64-66].

Compared with oral progestin, LNG-IUS in many studies has been found to have less severe systemic side effects and higher efficacy as a treatment for endometrial hyperplasia [66-71]. Gallos et al. [72] recently published a systematic review and meta-analysis of 24 studies that had compared endometrial hyperplasia regression rates between oral progestin and LNG-IUS for a total of 1,001 patients. In cases of simple hyperplasia, 213 women (9 studies) treated with oral progestin showed a pooled regression rate of 89%, versus the 96% rate for 72 LNG-IUS patients (6 studies). Meta-regression confirmed that these rates were not statistically

significant ($P=0.41$). In cases of complex hyperplasia, 389 patients (9 studies) administered oral progestin showed a pooled regression rate of 66%, versus the 92% rate for 102 LNG-IUS patients (4 studies). Overall, the treatment outcomes for LNG-IUS were statistically more significant than those for oral progestin ($P<0.01$). In atypical hyperplasia, 189 women (14 studies) treated with oral progestin showed a pooled regression rate of 69%, versus the 90% rate for 36 LNG-IUS patients (7 studies) ($P=0.03$) [72].

Lee et al. [73] reported on the effectiveness of LNG-IUS in 12 patients (4 simple, 7 complex, 1 atypical complex hyperplasia) evaluated at our institution in Korea. In all of the cases, complete regression of endometrial hyperplasia was achieved. The mean duration to regression was 4.5 months (66% achieved complete regression within 3 months), and all of the patients had achieved regression within 9 months. Additionally, a prospective multicenter trial on Korean women (planned number of patients: 80), this one by the Korean Gynecologic Oncology Group (KGOG2006), has been ongoing since 2006 [74].

Early-stage Endometrial Cancer

Endometrial carcinoma is the most common gynecologic malignancy in developed countries [75,76]. The majority of cases are diagnosed in postmenopausal women, and up to 14% of patients are premenopausal, among whom 3% to 5% are aged under 40 years, 70% of those 3% to 5% being nulliparous at the time of diagnosis [77,78]. On histologic examination, 84% of all endometrial cancers are endometrioid adenocarcinomas, which typically have a good prognosis [79]. Endometrial cancer in younger women usually is most commonly of the early clinical stage, well-differentiated and endometrioid type, which also carries a good prognosis [80]. The current standard treatment is total hysterectomy and bilateral salpingo-oophorectomy with or without surgical staging [81-83]. However, the data from multiple studies suggest that for select patients with early clinical stage carcinoma and a strong desire to maintain fertility, hormonal therapy is an attractive and effective alternative [84-88].

Progestins are the first medical treatment option for endometrial cancer. Progestins effect secretory differentiation of endometrial glands, inhibit estrogen receptor function and endometrial cell mitosis, and promote apoptosis; additionally,

some progestins have an anti-angiogenic effect [89]. According to a meta-analysis by Gallos et al. [90], a total 408 women (32 studies) who underwent fertility-sparing treatment by various methods, including progestin, LNG-IUS, GnRH agonist, aromatase inhibitor, and hysteroscopic resection, showed a pooled regression rate of 76.2%, a relapse rate of 40.6%, and a live birth rate of 28%.

Montz et al. [91] reported the results of LNG-IUS-based treatment of the International Federation of Gynecology and Obstetrics (FIGO) stage IA, grade 1 endometrioid cancer patients at high risk for perioperative complications. Among 12 patients, the biopsy results were negative for 64% at 6 months and 75% at 12 months. Cade et al. [92] reported on 16 patients who had been treated with MPA (4 patients), LNG-IUS (3 patients), or both (9 patients). Ten of the patients responded to treatment (MPA only, 2; LNG-IUS only, 1; both, 7), and the mean time to response was 5.5 months. The results of 5 young patients who had been treated, at our institution, with a daily 500 mg dose of MPA plus LNG-IUS insertion were published in 2010. Complete remission was achieved for 4 patients, and another one showed partial remission. During the mean 10.2 months follow-up period, there was no recurrence of disease [93]. Also in Korea, a prospective multicenter study (KGOG2009), initiated in 2009, has been treating patients with 500 mg of MPA plus LNG-IUS for early-stage endometrial cancer in young women [94].

Hormonal management with LNG-IUS and supplemental oral progestin appears to be a safe and moderately effective option for early-stage endometrial cancer patients who want to retain their reproductive potential. However, given that the relapse rate is higher than 40% [90], post-childbirth women should consider hysterectomy, which remains the standard of care.

Conclusion

The non-contraceptive benefits of LNG-IUS, particularly the effects on heavy menstrual bleeding and dysmenorrhea, as well as the option for 5-year use, add to its utility and efficacy as an alternative to long-term contraception. LNG-IUS in fact has proved to be an effective treatment modality for a great variety of gynecologic conditions: idiopathic, myoma- or adenomyosis-related HMB, endometriosis- or adenomyosis-related pelvic pain, as well as endometrial hyperplasia and early-stage

endometrial cancer. However, further large-scale randomized study and comparison with conventional treatment methods, along with long-term follow-up data, are needed.

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