Journal of Minimally Invasive Gynecology (2006) 13, 535–538

THE JOURNAL OF
MINIMALLY INVASIVE
GYNECOLOGY

Medicated intrauterine systems for treatment of endometriosis-associated pain

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KEYWORDS:
Levonorgestrel;
Intrauterine system;
Pelvic pain;
Endometriosis

Abstract. Medicated intrauterine systems (IUSs) are intrauterine devices that act by means of the local release of a medication. The levonorgestrel (LNG)-IUS is a T-shaped device that releases the progestogen LNG directly into the uterine cavity. The LNG-IUS can be used with noncontraceptive, therapeutic intent for idiopathic menorrhagia, hormonal replacement therapy in conjunction with oral or transdermal estrogens, and endometriosis or adenomyosis-associated pain. For this last indication, however, the use of the LNG-IUS is still under clinical investigation.

Medicated intrauterine systems (IUSs) are intrauterine devices (IUDs) that act by means of the local release of medication. In gynecology, the most-used IUSs are the progestogen-releasing devices, whereas the danazol-releasing devices are still under clinical development and not approved for general public use. The only LNG-IUS approved for clinical use is the Mirena (Berlex, Wayne, NJ), which releases 20 mcg of LNG per day during the first year, a rate that progressively decreases with time, reaching a rate of 11 mcg/day after 5 years. The commercially available LNG-IUS is intended for 5-year use. In Italy, the LNG-IUS is approved for clinical use for contraception, treatment of idiopathic menorrhagia, and hormonal replacement therapy in conjunction with oral or transdermal estrogens. In the United States, the device is approved by the U.S. Food and Drug Administration only for contraception. This review will briefly summarize the mechanism of action of the LNG-IUS and the evidence for its efficacy in idiopathic menorrhagia, and then review in detail the evidence for its efficacy for pain control in endometriosis.

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Submitted June 3, 2006. Accepted for publication June 10, 2006.

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doi:10.1016/j.jmig.2006.06.010

Mechanism of action of LNG-IUS

The levonorgestrel-medicated intrauterine system (LNG-IUS) acts by means of local release of LNG directly into the uterine cavity. After local release, LNG reaches concentrations many-fold higher in the endometrium than in surrounding tissues or plasma.[1]

In comparison with systemic administration, the local release of a drug should theoretically provide a similar or improved efficacy, particularly evident on the local target organ, with reduced systemic side effects. Efficacy and safety should also be matched to cost efficiency and acceptable patient compliance.

Locally, LNG may act by means of passive diffusion to the endometrial mucosa and by means of high concentration reached in the local venous and/or lymphatic circulation. High local LNG concentrations, matched with low systemic concentration, should provide high therapeutic efficacy with reduced side effects.

The main therapeutic action of LNG-IUS is through induction of endometrial atrophy, not through inhibition of ovulation. For complete inhibition of ovulation, in fact, a local release of 50 mcg of LNG is necessary,[2] which is more than twice the dose released daily by the LNG-IUS currently available. In LNG-IUS users, most menstrual cycles are ovulatory, particularly after the first year of use.[3] Even

in the presence of amenorrhea, the cyclicity of the pituitary is preserved, and ovulation occurs.[3] The effect of LNG as a cause of amenorrhea is therefore thought to be mainly of a local nature.

Side effects of the LNG-IUS can be divided into bleeding-related and not bleeding-related. Because the bleeding-related side effects are mainly attributable to the endometrium, where the locally released drug primarily acts, they are significant with the LNG-IUS. On the other hand, the side effects that are not bleeding-related, which are mainly due to the systemic concentration of the progestogen, may be reduced in comparison to systemically administered medications. Even though systemic concentrations of LNG remain low, some women still experience side effects such as acne, weight gain, headache, nausea, breast tenderness, depression and other mood disturbances. Unruptured follicle and ovarian cyst formation have also been reported with the use of the LNG-IUS.[2] To achieve higher compliance, patients should be informed of the possibility of menstrual disturbances with the LNG-IUS, which are the main reason for treatment discontinuation, and of the other progestogen-related side effects as well.

The use of the LNG-IUS for contraception goes beyond the scope of the present review. This review will report data only from a recent meta-analysis of randomized, controlled trials (RCTs) comparing medicated-IUSs versus nonhormonal intrauterine devices (IUDs) published by the Cochrane collaboration.[4] Women using LNG-IUSs releasing 20 mcg/day were no more or less likely to have unplanned pregnancies than women using IUDs greater than 250 mm^2, whereas LNG-IUSs were more effective compared with IUDs less than 250 mm^2. The LNG-IUS users were significantly more likely than all other IUD users to discontinue because of hormonal side effects and menstrual disturbances, amenorrhea in particular.[4]

With regards to the use of the LNG-IUS for contraception, we want to stress that the main contraceptive action of the LNG-IUS is its local effect on the endometrium. Ovulation occurs in a significant proportion of cycles, particularly after the first year of use, so this system may mainly act through an anti-implantation effect. Additional effect against conception may be provided by the LNG effect on cervical mucus, which becomes thick and scanty, making sperm penetration more difficult.[2] Other studies, however, reported minimal changes in cervical mucus, particularly in ovulatory cycles.[3] This information should be made clear to the patient who is using the LNG-IUS for noncontraceptive indications.

LNG-IUS for the treatment of menorrhagia

Among the various noncontraceptive, therapeutic indications for the LNG-IUS, treatment of menorrhagia is perhaps the one where most data are available today in the literature. Some early studies on the use of the LNG-IUS for contraception reported as a collateral result the improvement of associated menorrhagia and dysmenorrhea.[5] The strong endometrial suppression caused by the LNG-IUS results in a reduction of the amount of menstrual blood loss.

Various RCTs on the use of LNG-IUSs for the treatment of idiopathic menorrhagia, and also systematic reviews of such trials, have been published recently.[6] Overall, LNG-IUS reduces menstrual blood loss in patients with menorrhagia by 79% to 97%, with high patient satisfaction (72%–94%) and continuation rate (65–88%). However, many studies report a follow-up not extending beyond 1 year.[6,7]

In a systematic review published by the Cochrane Collaboration[6] on the use of progestogen-IUSs for the treatment of menorrhagia, LNG-IUS was significantly more effective in mean blood loss reduction compared with oral cyclic norethisterone administered from day 5 to day 26 of the cycle. Some short-term side effects were more common in the LNG-IUS group, but a significantly greater proportion of women in this group was satisfied and willing to continue the treatment. Compared with endometrial ablation (both with first- and second-generation ablation methods), LNG-IUS was associated with less reduction in mean blood loss in some trials, but the rates of patient satisfaction were similar. In the single RCT comparing LNG-IUS with hysterectomy, there was no evidence of a change in quality-of-life scores, but the LNG-IUS treatment had lower costs than hysterectomy, both at 1 and 5 years.

LNG-IUS for pain control in endometriosis

Patients affected by endometriosis may achieve improvement of associated pain symptoms with first-line medical treatment with nonsteroidal anti-inflammatory drugs or oral contraceptives.[8] When this first-line medical treatment fails, second-line therapy with danazol or gonadotropin-releasing hormone (GnRH) analogs may be started, even without surgical confirmation of disease.[8]

Due to the safety profile and side effects of the two drugs, however, both danazol and GnRH analogs can be used only for a short period of time, generally up to a maximum of 6 months. For longer treatment periods with GnRH analogs, "add-back" hormonal therapy usually must be added, thereby further increasing treatment costs.

Progestogens have been proposed as cost-effective alternatives to danazol and GnRH analogs because of their limited metabolic impact, high patient compliance, and low costs.[9] The high drug concentrations reached in the pelvic tissues with local release of progestogens with the LNG-IUS may further reduce side effects without reducing the therapeutic effects of the medication.

Medical treatment in the context of the management of endometriosis may be used either as primary therapy or as