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REVIEW

Non-contraceptive applications of the levonorgestrel intrauterine system

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Abstract: Intrauterine progestins have many important current and potential gynecologic applications. This article describes the evidence for use of intrauterine progestin for common gynecologic conditions beyond its important role in contraception. The pharmacology of and selection criteria for use of the levonorgestrel intrauterine device is discussed, and the evidence for use of intrauterine progestin delivery for menorrhagia, endometriosis management, uterine fibroids, adenomyosis and endometrial hyperplasia is reviewed.

Keywords: intrauterine progestin, levonorgestrel, contraceptive

Introduction

Progestins are available in a variety of formulations.[1] Intrauterine delivery of progestin is an effective way to administer local treatment and bypass systemic side effects. Intrauterine drug delivery has the potential to treat many gynecologic conditions, but is under utilized because clinicians lack knowledge and skills and because the only current delivery system (Mirena®; Bayer HealthCare) is unavailable or costly in many countries.[2]

Progesterone is a key hormone in regulating the female reproductive system, interacting at the level of the hypothalamus, the ovary, the uterus and the breast. Progesterone exerts effects on ovulation, endometrial differentiation, cervical mucus, breast differentiation and uterine contractility.[1,3] Progestins and their analogs and antagonists have many uses in gynecology including contraception, management of miscarriage, medical abortion and treatment of conditions related to endometrial and myometrial growth and development. Beyond providing highly effective contraception, intrauterine delivery is safe and effective in the management of menorrhagia, dysmenorrhea, uterine myomata, and endometrial proliferation.[4]

We describe the evidence for use of intrauterine progestins for common gynecologic conditions in addition to their important role in contraception; we also review the evidence for use of intrauterine progestin delivery for menorrhagia, endometriosis management, uterine fibroids, endometrial hyperplasia and its concurrent use in women on hormone replacement therapy or tamoxifen.

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Pharmacology

Many different progestins are used in oral and implantable contraceptives, however only one form of intrauterine delivery is currently approved for use by regulatory agencies. The levonorgestrel intrauterine system (LNG-IUS, Mirena®) is a T-shaped device, with a reservoir containing 52 mg of levonorgestrel. In vivo, the hormone is

released at an initial rate of 20 mcg daily, which progressively declines to half this rate by 5 years.[1] Levonorgestrel is a 19-nortestosterone derivative and exhibits a profound progestational effect on the endometrium.[5] The endometrial lining becomes atrophic and inactive and cervical mucus becomes thick and scant.[1] Approximately 80% of cycles are ovulatory.[1]

With the intrauterine system, levonorgestrel dose is concentrated in the endometrial cavity. The most frequently noted side effects, irregular bleeding and cramping, are due to the intrauterine location of the device and endometrial atrophy. A common concern with hormonal contraceptives is their effect on coagulation and thromboembolic events.[1] With the LNG-IUS, serum levels are a fraction of the endometrial dose, and in the first 2 months following insertion have been measured in the pico gram range (86–760 pg).[6] Large epidemiologic studies have not demonstrated an increased risk in clot formation with oral levonorgestrel at much higher serum concentrations.[7]

Patient selection is important factor in predicting success. Nulliparity is not a contraindication to placement.[8] Ideally the uterus should sound between 6 and 9 cm. Uterine anomalies can compromise success by increasing expulsion rates and risk of perforation.[1]

Menorrhagia and the levonorgestrel intrauterine system

Menorrhagia is excessive blood loss with menstruation (greater than 80 mL blood loss or menses lasting longer than 7 days duration) and is a common gynecologic complaint.[9] The prevalence of menorrhagia increases through the perimenopausal period. Menstrual disorders affect 10% to 15% of women and are a common indication for hysterectomy in the US.[9,10] One-third of women in the US undergo a hysterectomy, a rate much higher than in Western Europe.[10] This difference may be due in part to lower utilization of the LNG-IUS to control menorrhagia in the US, despite excellent evidence that exists to support its use. Hysterectomy is a major surgery, and entails greater risks and costs than medical treatment. While hysterectomy remains a viable option for menorrhagia refractory to medical management, the LNG-IUS is underutilized to control menorrhagia.

The LNG-IUS has been evaluated for its impact on menstrual blood loss and acceptability as an alternative to hysterectomy.[9,11–15] Menstrual blood loss with the LNG-IUS was reduced by 86% at 3 months, and 97% at 6 months, and parameters of anemia such as hematocrit and ferritin levels improved.[13] The reduction in menorrhagia noted with the LNG-IUS is superior to that reported from all other forms of medical management, including use of oral contraceptives, tranexamic acid and prostaglandin synthetase inhibitors.[10]

The LNG-IUS has also been compared to a variety of ablative techniques. Endometrial ablation is a commonly used procedure in the surgical management of menorrhagia.[16] A range of techniques and devices are available for endometrial ablation. The thermal balloon is a popular global ablation device that allows transcervical destruction of the endometrium.[16] The LNG-IUS has been compared with thermal balloon ablation and manual hysteroscopic ablation for reduction of blood loss, patient satisfaction, and cost.[16–18] At 12 and 24 months of follow up, women treated with the LNG-IUS had significantly higher rates of amenorrhea than the ablation group ($P = 0.025$). A recent meta-analysis of 6 randomized controlled trials comparing the LNG-IUS to endometrial ablation showed that outcomes, including quality of life measures, were comparable between the two methods at two years of follow up.[19] Cost effectiveness analysis also supports the LNG-IUS as preferable in terms of direct and indirect costs to thermal balloon ablation.[17]

The acceptability for patients of a LNG-IUS in place of hysterectomy has been studied in women with menorrhagia. Women in Finland awaiting a scheduled hysterectomy for menorrhagia were randomized to either LNG-IUS insertion or to continue their current medical management.[21] The primary outcome was the proportion of women cancelling hysterectomy at 6 months, which was the average wait time for a hysterectomy in Finland during the study period. At 6 months, 64% of women in the LNG-IUS group had decided against hysterectomy as compared to 14% of the control group ($P < 0.001$).[20] Five-year follow up of women randomized to LNG-IUS or hysterectomy showed equal satisfaction with treatment outcomes in both groups, but lower costs in the LNG-IUS group.[21]

Endometriosis and the levonorgestrel intrauterine system

Endometriosis, the presence of endometrial cells outside of the uterus, is the most common diagnosis among chronic pelvic pain patients, and affects 7% to 20% of all women.[5] In addition to chronic pelvic pain, endometriosis is associated with infertility.[5,22] Therapy for endometriosis is both medical and surgical. Surgical ablation of implants as well as use of medical therapies such as non steroidal anti-inflammatory drugs, progestins like depot medroxyprogesterone acetate, continuous oral contraceptives, gonadotropin releasing

hormone analogs (GnRHa) to induce a pseudo menopause, and androgen derivatives are the mainstays of treatment.[5] The medications that elicit the most profound improvement have systemic side effects such as estrogen deprivation, which limit the duration of their use.

The role of the LNG-IUS in management of this common and debilitating disorder has been evaluated by multiple studies.[5,23–25] A pilot study examined the role of LNG-IUS as a postoperative adjunct to surgical ablation for endometriosis.[26] When compared with expectant management, the LNG-IUS recipients had a reduced rate of recurrence of pelvic pain (2/20 compared with 9/20) and an increased rate of satisfaction (15/20 compared with 10/20).[26] Similarly, a randomized controlled trial comparing LNG-IUS to medical therapy with a GnRHa had promising results.[25] Eighty-two women with surgically confirmed endometriosis were randomized to LNG-IUS or GnRHa and, using visual analog scores (VAS), pain and bleeding patterns were assessed at baseline and at 6-month intervals. At 36 months, 59% of women were still using the LNG-IUS and 82% of these users reported a lower VAS score compared with GnRHa.[23]

A prospective study followed 34 women with laparoscopically confirmed early stage endometriosis who had an LNG-IUS placed at time of surgery.[27] Patients were followed for 3 years and continuation rates, pain scores and bleeding rates were assessed at regular intervals and compared to baseline levels.[27] Significant improvements in all parameters were noted at 12 months, with an improvement in pain (recorded by visual analog score) from 7.7 at baseline to 3.5 at 12 months and 2.7 at 36 months ($P < 0.02$).[27] While this study's findings are limited by its lack of controls, small cohort and high discontinuation rate (32% at 12 months, most commonly for irregular bleeding), it shows promise and further research should be conducted.

The LNG-IUS offers several advantages for control of pelvic pain associated with endometriosis including effective contraception, minimal systemic effects and up to 5 years of benefit, as compared with 6 months typical of GnRHa treatment.

Uterine fibroids and the levonorgestrel intrauterine system

Uterine leiomyomas and their clinical sequelae are a common gynecologic problem, as fibroids are present in approximately 25% of reproductive aged women.[28] While leiomyomas may be asymptomatic, they can be associated with heavy menstrual bleeding, dysmenorrhea, pelvic pressure, and obstructive symptoms such as urinary frequency and constipation.[29] Symptoms from leiomyomas may be managed with medical therapy, but they remain the most common indication for hysterectomy in the US.[29] The uterine location of the myomas – subserosal, intramural or submucosal – effects the clinical sequelae. Subserosal locations are more commonly associated with obstructive symptoms, while submucosal are correlated with heavy menstrual bleeding.

The LNG-IUS has been studied in women with leiomyomas, specifically in relation to acquired menorrhagia, uterine volume, and expulsion rates.[29–31] Fewer studies have assessed relief of obstructive symptoms or dysmenorrhea.

The beneficial effect of the LNG-IUS on acquired menorrhagia due to a leiomyomatous uterus is well established. In prospective trials, the LNG-IUS has significantly decreased menorrhagia from fibroids, as measured by pictorial blood loss assessment, hemoglobin levels, and blood loss calenders.[28,30,32–36]

Intrauterine progestin has been compared to ablation in the treatment of menorrhagia in patients with at least one myoma.[34] A cohort of women with menorrhagia and a leiomyomatous uterus (<380 g) who declined surgery, were treated with an LNG-IUS. Patients were evaluated at 3, 6 and 12 months and compared to historical controls treated with thermal balloon ablation.[34] At 3 months, blood loss was significantly less in the ablation group ($P < 0.0001$). By 6 months, however, there was no statistically significant difference in hemoglobin values, pictorial blood loss score or uterine volume between the two groups. These findings persisted at the 12-month examination.[34]

Not all women with myomas are successfully treated with the LNG-IUS, perhaps because response is determined by the fibroids' uterine location. In an attempt to identify factors predictive of non response to the LNG-IUS, 44 women presenting for hysterectomy after failed LNG-IUS management for menorrhagia were studied.[37] Persistent menorrhagia was the indication for the majority (44 out of 50). Women were retrospectively identified and their pathology reviewed. Examination of the histology demonstrated that the majority of women who failed therapy with an LNG-IUS and fibroids had an abnormal uterus.[37] Uterine malformations, such as submucosal fibroids, was the most common finding, although a unicornuate uterus and an LNG-IUS embedded in an old cesarean scar were also noted.[38] These specimens showed the expected atrophy, but also contained some areas of persistent endometrial shedding deemed to be consistent with incomplete endometrial suppression.[37] Durations of exposure to the LNG-IUS were not specified in the report of

this study, which is a chief limitation in assessing the impact of the LNG-IUS.

Studies have evaluated the effect of LNG-IUS on leiomyoma size, but findings have not been consistent. Using sonographic measurements, Grigorieva et al found a significantly decreased uterine volume in LNG-IUS users starting at 3 months after placement and persisting through 12 months.[30] They also found a significant decrease in leiomyoma size from 6 months to 12 months of use (30–19 mL, $P = 0.01$). A study comparing the effect of LNG-IUS on menorrhagia in women with fibroids and contraceptive users without fibroids also showed a significant decrease in uterine volume over time and between groups.[38]

Evidence of the outcomes of intrauterine progestin on fibroids comes indirectly from a trial comparing women with a history of breast cancer and receiving tamoxifen. These patients were randomized to endometrial surveillance alone, or insertion of LNG-IUS for prophylaxis of endometrial hyperplasia.[39] Sonographic uterine measurements showed that women with the LNG-IUS had decreased endometrial thickness, uterine anterior posterior diameter, uterine cavity length and long diameter. At 1 year of use, endometrial thickness and myoma volume were significantly decreased ($P = 0.04$).[40] A trend towards decrease in size of submucosal fibroids in the LNG-IUS users and a significant increase in the development of fibroids in the control group were also noted.

A 2009 Turkish prospective cohort study assessed the impact of the LNG-IUS on uterine and ovarian volume. At one year of use, endometrial thickness and myoma volume were significantly decreased ($P = 0.04$).[31,40]

In contrast, other studies have not shown a significant decrease in uterine volume with an LNG-IUS, despite a consistently significant decrease in blood loss scores.[34,41] These conflicting findings probably reflect study design, specifically length of follow up and inclusion and exclusion criteria. However, it has also been suggested that progesterone may have both stimulatory as well as inhibitory effects on myometrial cells.[37] Further research is needed to elucidate the role intrauterine delivery of progestin analogues may play in leiomyoma volume. For the well-counseled patient with menorrhagia secondary to uterine leiomyomas, a trial of the LNG-IUS is supported by the evidence.

Endometrial hyperplasia and the levonorgestrel intrauterine system

Given the profound endometrial atrophy the LNG-IUS induces, its potential for management of endometrial hyperplasia has been investigated.[42–44] Endometrial hyperplasia ranges from simple to complex, with or without atypia and is considered a precursor of endometrial cancer.[44] In the presence of atypia, risk of progression to cancer is estimated at 30%, thus the standard of care in women who have completed childbearing is hysterectomy for hyperplasia with atypia.[45] For women who wish to preserve fertility, or who have hyperplasia without atypia, or are poor surgical candidates, oral or depot progestin therapy is typical.[43,45] Controversy exists about the appropriate length of time of treatment and the dosage of oral therapy.

Treatment response to oral and intrauterine progestins has been compared in groups with endometrial complex hyperplasia with atypia and well differentiated carcinoma.[45] Both groups responded well to therapy with no statistical difference between therapy route when menopausal status was controlled for. For women with complex atypical hyperplasia, 67% had complete resolution, 11% regressed to complex hyperplasia without atypia, and 22% had persistent disease over 11 months.[46] For women with well differentiated carcinoma, 42% completely resolved and 58% had persistent disease over a 12-month period.[45] Of note, no patients with persistent atypia on biopsy at 7 months ultimately regressed or resolved. While a small sample size precludes definitive conclusions, this study suggests that minimal benefit is obtained for continuing to treat patients with atypia on biopsy with more than 7 months of medical therapy and no significant difference in efficacy exists between oral and intrauterine therapy. The LNG-IUS has been contrasted with standard oral therapy and found to equal or surpass it.[43,46,47] Orbo et al, report a prospective trial contrasting low dose oral progestin therapy with LNG-IUS. A total of 258 women with endometrial hyperplasia were randomized to either intrauterine or oral treatment. The D score classification was used to characterize histological findings consistent with risk for progression. At 6 months of follow up, patients in the LNG-IUS arm had significantly higher rates of regression.[46] Long-term follow up occurring at 58 to 106 months was notable for higher rates of regression in those with intrauterine treatment.[46]

In observational studies of women with hyperplasia (both with and without atypia) regression was achieved by the majority receiving LNG-IUS treatment.[43,44,50] The largest study, by Varma et al, was a prospective observation of 105 women with endometrial hyperplasia.[48] Women were included in the study if they had non atypical hyperplasia and selected an LNG-IUS over oral therapy. Women with atypical hyperplasia were only

included in the study if they were not surgical candidates.[43] Their hyperplasia was regularly assessed by endometrial biopsy with the LNG-IUS in place. A 90% regression of hyperplasia was noted by 24 months (94/105 patients).[43]

Tamoxifen and the levonorgestrel intrauterine system

Tamoxifen is the adjuvant therapy of choice for patients with estrogen receptor positive breast tumors.[49] Tamoxifen has a proliferative effect on the postmenopausal endometrium, resulting in a higher incidence of endometrial pathology.[49,50] The increased risk of developing endometrial cancer for a woman on tamoxifen is 2 to 3 times that of an age-matched control.[51] Management of the asymptomatic, postmenopausal patient on tamoxifen is controversial.[51]

A randomized, controlled trial evaluated the impact of a prophylactic LNG-IUS compared with observation in women undergoing tamoxifen therapy after breast cancer surgery. One hundred and thirteen women were enrolled and followed for 12 months. Comparison of endometrial biopsies at 12 months revealed that the LNG-IUS patients had a much lower relative risk for formation of endometrial polyps (0.12, confidence interval 0.02–0.91).[52] The LNG-IUS was a well accepted intervention, with 95% retention at 1 year.[52]

In another study, 142 postmenopausal women on tamoxifen after breast cancer treatment were randomized to either the LNG-IUS or observation and followed with endometrial biopsies and blood draws for 3 years. Of this group, 70 had an LNG-IUS and 72 had observation during standard tamoxifen therapy. Six were excluded from analysis due to inability to insert the device. At 36 months of follow up there were no statistically significant differences between the two groups in serum lipid profiles, but a significant difference in endometrial pathology was seen at follow up biopsy. In the control group, endometrial polyps were found in 14 patients and endometrial hyperplasia in 4. Among the women treated with an LNG-IUS, 4 had polyps but none had hyperplasia ($P < 0.05$).[50]

These long-term results from two small trials show promise for the LNG-IUS as a means of reducing endometrial pathology associated with tamoxifen.

Conclusion

Progestin plays a critical role in gynecologic treatments beyond their current use in contraception. Intrauterine delivery is an effective localized therapy, and intrauterine progestin has many important applications in managing gynecologic conditions such as menorrhagia, endometriosis, leiomyomas and endometrial hyperplasia.

Disclosures

Dr Philip Darney conducts research for and is a consultant for Bayer Pharmaceuticals.

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