

Endometrial suppression with a new “frameless” levonorgestrel releasing intrauterine system in perimenopausal and postmenopausal women: a pilot study

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Abstract

A novel intrauterine drug delivery system, FibroPlant-levonorgestrel (LNG), derived from the frameless GyneFix intrauterine device (IUD) is described and the preliminary results in 30 symptomatic climacteric and postmenopausal women are discussed. The treatment with the FibroPlant-LNG intrauterine system (IUS) was instituted to suppress the endometrium during estrogen substitution therapy (EST) to prevent endometrial proliferation and bleeding. The purpose of the study was to evaluate the clinical and ultrasonographic effect of this new intrauterine progestin delivery system. Two dosage forms were tested: the first 11 women received a 3-cm long coaxial fibrous delivery system, delivering approximately 10 µg/day of LNG; the remaining 19 women in the study received a 4-cm long delivery system, delivering approximately 14 µg/day. The calculated duration of release of the two systems is approximately 5 years.

Twenty-two women were perimenopausal at the start of the treatment. Women in this study were observed during at least one year. Most postmenopausal women received percutaneous 17β-estradiol (Oestrogel), 1.5 mg daily on a continuous basis.

Results: All postmenopausal women in the 2 groups reported amenorrhea during the entire study period (up to 2 ½ years follow-up). Endometrial atrophy in these women was confirmed by vaginal ultrasound examination. Seventeen of 22 perimenopausal women reported amenorrhea at the first or second follow-up visit at 1 and 3 months following insertion of the IUS, respectively. The remaining had infrequent scanty bloody discharge needing a panty liner, at the most, for protection.

There were no complications in this study (e.g., infection, expulsion or perforation). The FibroPlant-LNG IUS is very well tolerated by all women and no systemic hormonal side effects were reported. There were no removals for medical reasons.

Conclusion: The results of this pilot study suggest that the frameless FibroPlant-LNG IUS is safe, well tolerated and effective in suppressing the endometrium during EST. No differences could be clinically distinguished between the 2 dosages. Compliance was optimal. The fact that the IUS also acts as a potent contraceptive is of added importance.

Keywords: Intrauterine drug delivery system (IUS), levonorgestrel, hormone substitution therapy, contraception

Introduction

Natural progesterone and its derivatives are prescribed in combination with estrogen substitution therapy (EST) to protect the endometrium from the hyperplastic and potentially cancerous effects of prolonged, unopposed EST. However, they have an essentially anti-estrogenic effect and can potentially counteract the beneficial effects of co-administered estrogens. In addition, they may precipitate a number of hormonal side effects such as mood changes, headache, sleepiness, mastalgia, nausea, hirsutism. Progestins affect the arterial function in a state of vasomotor instability. They also induce vasoconstriction of estrogenized vessels.¹ Some studies have been reassuring in this respect.²⁻⁴ The main concern, however, about progestins compromising the cardioprotective actions of estrogens rests in the recognition that estrogen effects on the arterial physiology are important in preventing ischemic events and that progestins could have an adverse effect on these actions.^{5,6}

Consequently, it has been proposed that the best method for delivering a progestin to postmenopausal or climacteric women would seem to deliver it directly to the target structure, the endometrium, to avoid systemic effects.^{7,8}

The FibroPlant-LNG delivery system was developed to provide just such a localised effect. The system has further been optimized to provide optimal tolerance, thereby avoiding incompatibility problems commonly seen with conventional IUDs and with the T-shaped LNG-IUS (Mirena[®]). The study with a follow-up of 12 to 28 months was conducted to

evaluate the clinical performance respectively of a 10 µg/d and 14µg/d levonorgestrel-releasing implant system and to study their effect on the endometrium by ultrasound.

Materials and methods

Description of the FibroPlant-LNG IUS

The FibroPlant-LNG IUS consists of the standard GyneFix anchoring system but has no copper tubes attached to the thread. Instead, a 3-cm long and 1.2 mm wide fibrous delivery system, releasing approximately 10 µg of LNG per day (first 11 women), or a 4-cm long and 1.2 mm wide fibrous delivery system releasing approximately 14 µg of LNG per day (remaining 19 women), is fixed to the anchoring thread by means of a metal clip 1 cm from the anchoring knot. Based on in vitro study, the rate of release is constant over several years (zero-order). The duration of release, calculated by extrapolation, is approximately 5 years. The fibrous delivery systems were developed in collaboration with the Polymer Research Group, University of Ghent, Department of Chemistry, Ghent, Belgium.

The anchoring knot is implanted into the myometrium of the uterine fundus using the GyneFix insertion instrument, so permanently securing the implant in the uterine cavity (Figure 1). The metal clip allows visibility of the system on ultrasound and X-ray, enabling proper location of the system in the uterine cavity at insertion and on follow-up. The fibrous delivery system is also visible on ultrasound (Figure 2). Measuring the distance between the surface of the uterus and the metal clip (S-S distance) indicates whether the FibroPlant IUS has been properly anchored. In contrast with framed drug delivery systems, such as the LNG-IUS Mirena[®], the FibroPlant-LNG IUS has no frame, it is completely flexible, adapting to cavities of every size and shape.

Admission

All insertions were done by the same investigator (DW). Written informed consent was obtained and the study was approved by the Ethics Committee of the University in Ghent, Belgium. Prior to the insertion procedure, a medical history was taken and pelvic examination was carried out and the patient checked for any clinical signs of sexually transmitted diseases. Since women included in the study were at low risk for sexual transmitted diseases (STIs), no routing chlamydia tests were done. All women were screened for their clinical suitability for

IUD insertion and compliance with the eligibility criteria. The following were excluded: clinical cervicitis or vaginitis (infection should be ruled out); sound length greater than 10 cm; history of PID, genital actinomycosis or chronic pelvic pain; blood clotting disorder and / or undiagnosed genital tract bleeding; known or suspected uterine or cervical malignancy including unresolved, abnormal PAP smear; large (in the investigator's judgement) uterine fibromata; congenital malformation of the vagina, cervix or uterus; postpartum endometritis or history of infected abortion; leukemia; currently receiving corticosteroid or immunosuppressive therapy; congenital valvular heart disease. Only women with normal genitalia were admitted in the study. The endometrial status was evaluated by transvaginal or abdominal ultrasound examination prior to insertion of the implant system. In the event that the uterus was found to be atrophic (presence of basal and parabasal cells on wet vaginal smear), EST was started immediately and the insertion of the FibroPlant system was postponed until the uterus was sufficiently primed. This was not necessary in all perimenopausal women included in the study. All insertions were done without local anaesthesia or the use of analgesics. Insertion of the FibroPlant IUS is identical to the insertion of the GyneFix implant system.⁹

Perimenopausal women were defined as women with increasing menstrual irregularities or amenorrhea less than 12 months but more than "their normal" cycle length.¹⁰ The transdermal route was the preferred mode for administering the estrogen. Eight women were postmenopausal at the start of the study and received percutaneous 17 β -estradiol (Oestrogel), 1.5 mg daily on a continuous basis to treat their menopausal symptoms. Twenty-two women were perimenopausal at the start of the treatment. The majority of them received Oestrogel at a continuous dosage of 1.5 mg daily. Some of these women received a lower dosage (0.75 mg/day) according to their need as they still had residual ovarian function. This dosage was increased if the menopausal symptoms were not completely suppressed or if parabasal cells were still present on the vaginal smear.

All FibroPlant insertions were done to suppress the endometrium. Following insertion, gentle traction on the tail of the IUS was exerted to feel if the anchor was properly fixed. A vaginal ultrasound was performed (Ultramark[®] 4Plus) to locate the device in the uterus and to measure the distance between the metal clip and the serosa of the uterus (S-S distance) as described previously.⁹

Follow-up

Women were followed-up at 1, 3, 6, and 12 months following insertion of the IUS and 6-monthly thereafter. They were asked about their bleeding pattern and about any side effects or adverse reactions. A gynecological examination was performed as well as a vaginal ultrasound to locate the implant and to evaluate the thickness of the endometrium according to Fleischer and Kepple.¹¹

Results

Between April 1997 and December 1998, 30 FibroPlant-LNG implant systems were inserted in symptomatic perimenopausal and postmenopausal women. The patients were split in 2 groups: the first 11 women entering the study received a 10 µg/day LNG-releasing IUS, the remaining 19 women a 14 µg/day releasing IUS. Eleven FibroPlant systems were inserted in perimenopausal women immediately after removal of the GyneFix implant system. Since the number of insertions is small, no statistical analysis was performed. The events were evaluated on an individual basis. Table 1 shows the characteristics of the group and table 2 the clinical events in the 2 groups combined.

Table 1. Characteristics of the FibroPlant IUS users: Age distribution

	10 µg	14 µg
Average Age	52.5	52.4
Lowest Age	43	48
Highest Age	61	57

Table 2. Events in the 30 FibroPlant-LNG users

Events	n	%
Removals		
Investigator's choice*	5	16.66
Lost to follow-up	0	0.0
Total No of terminations	0	0.0
Continuation of use	25	83.33
Total women-months	512	
Min. women-months	12	
Max. women-months	28	
No of women	30	

* Systematic removal after 2 years to assess residual content of steroid

By the end of December 1999, the 30 recruited women had at least one year follow-up. All women had an atrophic endometrium (< 5 mm in thickness), as judged by ultrasound (Figure 2). No hormonal side effects were reported. After an initial short period of spotting, menstrual bleeding stopped completely or almost completely in all women studied. Slight scanty and infrequent bloody discharge requiring no protection, or a small panty liner, occurred in 5 women during the first 6 months of treatment. In two women, it took somewhat longer to become amenorrheic. There were neither adverse reactions (e.g., pelvic inflammatory disease, perforation), expulsions, nor accidental pregnancies recorded in this study. No complaints of abdominal pain were reported by users of the FibroPlant-LNG systems. In 5 women, the system was removed after 2 years to assess the residual content of the steroid in the delivery system. These women were fitted immediately with a new FibroPlant-LNG system but not re-admitted in the study. All women are continuing to use the method and are free of side effects. Ultrasound evaluation on follow-up examination: The average distance from the serosal surface of the uterus to the metal clip (S-S distance) was 15.3 (range 12-20 mm). The endometrium became atrophic (< 5 mm) in the two groups of women in the study at the first (at 1 month) or second follow-up visit (at 3 months). No apparent difference was noticeable between the two groups of women.

Discussion

The purpose of the study was to evaluate the FibroPlant-LNG IUS clinically and by ultrasound in a small number of perimenopausal and menopausal women receiving two different dosage forms.

The results of this pilot study suggest that the FibroPlant-LNG system, releasing either 10 µg of LNG per day or 14 µg of LNG per day, is a safe and effective method for suppressing the endometrium during EST in perimenopausal and menopausal women resulting in atrophy of the endometrium and amenorrhea in the majority of women. No differences in the endometrial effect between the two dosage forms could be detected by ultrasound examination. Slight scanty bloody discharge can occur, mainly in perimenopausal women but is infrequent and of little significance. The added advantage of the locally delivered LNG is its strong contraceptive effect. Although fertility of perimenopausal women is reduced, when compared with younger women, the risk of pregnancy is still present.

The average fundal myometrial thickness (15.3 mm) was significantly thicker than the fundal thickness reported in younger women (average S-S distance 12.7 mm).⁹

The daily intrauterine release of levonorgestrel is low. This may explain the absence of side effects which are more likely when higher dosages are used as with the Mirena[®] IUS.¹² Whether a small fraction of the hormone, delivered by the FibroPlant-LNG IUS, is absorbed in the peripheral circulation or not needs to be further elucidated. This is expected to be limited as has been demonstrated with the Mirena[®] IUS.¹²

The FibroPlant system is a further development of intrauterine drug delivery systems exploiting the benefits of the atraumatic frameless design, which minimizes the side effects and discomforts which perimenopausal and menopausal women may experience with conventional IUDs and current intrauterine steroid delivery systems due to incompatibility.¹⁰ The small and flexible FibroPlant-LNG system is extremely simple and completely in harmony with the uterus; perhaps this is one of the main advantages of this new intrauterine LNG-delivery system.

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