European J of Contraception & Reproductibve Health Care 2000;5:234-240

Contraception with a novel "frameless" intrauterine levonorgestrel-releasing drug delivery system: A pilot study

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ABSTRACT

Objective To evaluate the contraceptive performance, acceptability, side-effects and adverse events of a novel "frameless" intrauterine drug delivery system (IUS), FibroPlant-levonorgestrel (LNG), releasing 14µg of LNG/d. An ancillary objective being to evaluate the effect of the new IUS on menstrual blood loss.
Study design An open label, non-comparative ongoing pilot study. Fifty-four insertions were performed in fertile women between16 and 51 years of age for contraception by the first author. From these, 18 women were fitted with the FibroPlant-LNG IUS for the treatment of excessive bleeding as well as for contraceptive purposes. Twelve of these women had medium to large size uterine fibroids in addition to heavy menstrual flow. The trial covers a period from a minimum of 6 months up to 16 months.
Results At the time of study analysis the total number of women-months was 464. Twenty-one women having the FibroPlant-LNG IUS in place for periods in excess of one year. No pregnancies occurred. All women reported greatly reduced bleeding, however no cases of amenorrhea resulting from endometrial suppression were encountered.
Significant spotting was rare after the first three months following insertion. No complications (e.g., infection, expulsion or perforation) occurred. The FibroPlant-LNG IUS was well tolerated by all women involved in the study and no systemic hormonal side-effects were reported.
Conclusion Although the average age of women included was 40, this preliminary study suggests that FibroPlant-LNG IUS is an effective contraceptive. The FibroPlant-LNG IUS is also highly efficacious in controlling bleeding in women presenting with excessive menstrual flow. Effective endometrial suppression is the principal mechanism underlying both the contraceptive effect and it's effect on menstrual blood loss.
The low release rate of levonorgestrel results in an absence of hormonal side-effects. The unique "frameless" design characteristics of the IUS facilitates insertion and minimises reports of pain and discomfort. These factors, together with the low incidence of amenorrhea appear to be a significant step forward from the 'framed' Nova-T LNG-IUS (Mirena®).

KEY WORDS: "Frameless" intrauterine system (IUS), Levonorgestrel (LNG), contraception, Menorrhagia, Pilot study

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INTRODUCTION

The FibroPlant-LNG intrauterine system (IUS) was designed to maintain the advantageous effects of the 20 µg/day levonorgestrel (LNG)-releasing IUS (Mirena®) (Schering AG, Berlin, Germany) whilst addressing reported difficulties in insertion and reducing troublesome side-effects such as, disturbed bleeding patterns, amenorrhea and hormonal side-effects.[1] The FibroPlant-LNG intrauterine system is a further development of the "frameless", copper bearing GyneFix® intrauterine contaceptive device. The FibroPlant-LNG IUS uses the same anchoring technology that has been *shown in practice* to be compatible with uterine cavities of all shapes and sizes.

Clinical results with the GyneFix® implant are described and published elesewhere.[2-5] The FibroPlant-LNG IUS is anchored in the uterine cavity in a similar manner to the "frameless" GyneFix IUCD to minimise expulsion. This is important as published statistics show that at least 5% of 'framed' IUDs/IUS are expelled during the first year of use.[6,7]

The FibroPlant-LNG IUS has been developed in order to provide a pure localised effect of endometrial suppression. The localised activity of LNG is many times stronger than the effect obtained following oral treatment. It is this enhanced activity that could be useful for the intrauterine treatment of menorrhagia. Furthermore, LNG delivered in the uterine cavity provides a strong contraceptive effect.[1]

The provision of both contraception and treatment is a highly desirable combination in young women. It is also extremely valuable in women in the 35-40 age group where the occurrence of menorrhagia is more prevalent than at a younger age.

The physical design of the FibroPlant-LNG IUS has been optimized in order to provide optimal tolerance, and thereby avoid the incompatibility problems frequently encountered with conventional IUDs and the T-shaped LNG-IUS (Mirena®).[2,8]

The lower release rate of FibroPlant-LNG (14 µg/day) when compared with the Mirena® IUS (20 µg/day) could account for the overall low rate of side-effects found with FibroPlant-LNG. Specifically this includes the occurrence of amenorrhea and a reduced or absent effect on ovarian function.

The study with a follow-up period of between 6 months and 16 months was conducted to evaluate the contraceptive performance of the FibroPlant-IUS and to study its effect on the endometrium by ultrasound.
This is the second clinical study conducted with the FibroPlant-LNG IUS. The first study evaluated the endometrial suppressive effects of FibroPlant-LNG in perimenopausal and postmenopausal women during estrogen replacement therapy.[9]

MATERIALS AND METHODS

Description of the FibroPlant-LNG IUS

The FibroPlant-LNG IUS uses the standard GyneFix® anchoring system but has no copper tubes attached to the thread. The copper tubes being replaced by a 4-cm long and 1.2 mm wide fibrous delivery system that releases approximately 14 μg of LNG daily. The fibrous delivery system is fixed to the anchoring thread by means of a metal clip positioned 1 cm from the anchoring knot.
In vitro study show that the rate of LNG release is constant over several years (zero-order). The duration of release, calculated by extrapolation, is approximately 5 years.[10]
The fibrous delivery system was developed in collaboration with the Polymer Research Group, Department of Chemistry, University of Ghent, Ghent, Belgium.

In common with GyneFix®, the anchoring knot at the proximal end of the thread is implanted into the myometrium of the uterine fundus using the standard GyneFix® insertion instrument, thus permanently securing the implant in the uterine cavity (Figure 1).
The stainless steel metal clip allows ultrasound and X-ray visibility of the system thus enabling correct location of the system in the uterine cavity, both at insertion and at 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.
When compared with "framed"drug delivery systems such as the LNG-IUS Mirena®, the FibroPlant-LNG IUS will be seen to have no frame, it is therefore completely flexible, with the ability to adapt to uterine cavities of every size and shape.

Admission and insertion of the IUS

One investigator (DW) performed all insertions. Written informed consent was obtained from patients and the Ethics Committee of the Ghent University, Belgium approved the study.
A full medical hsitory was taken prior to the insertion, pelvic examination was carried out, and the patient checked for any clinical signs of sexually transmitted diseases. Routine chlamydia tests were not carried out as those women included in the study were at low risk for sexually transmitted diseases (STIs).
All women to be included in the study were screened for both their clinical suitability for IUD insertion and compliance with the WHO eligibility criteria. The following were excluded: use of any other form of contraception; 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; known or suspected uterine or cervical malignancy; 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.
Investigation of excessive menstrual bleeding was limited to office gynaecological examination including vaginal ultrasound examination (Ultramark® 4Plus). Neither hysteroscopy nor endometrial biopsy were carried out routinely. Fibroids were categorized as small, medium or large. Fibroids larger than the size of a uterus of 12 weeks gestation were not admitted in the study. Most fibroids were subserosal or intramural. Wherever possible, the regularity of the uterine cavity was checked during sounding of the uterus to check the presence of intracavitary fibroids prior to insertion of the IUS.

Local anaesthesia (intracervical anaesthesia with dental syringe) was used only in nulliparous and anxious women to increase comfort.
Insertion of the FibroPlant IUS is identical to that for the insertion of the GyneFix® implant system.[1]

Following insertion, gentle traction was exerted on the tail of the IUS to ensure that the anchor was properly engaged. A vaginal ultrasound was performed to locate the device in the uterus as described previously.[1]

Follow-up

Women were followed-up at 1, 3, 6, and 12 months following insertion of the FibroPlant-LNG IUS and 6-monthly thereafter. During follow-up interviews/questions were asked about their bleeding patterns and any side-effects or adverse reactions. On each occasion a full gynecological examination including vaginal ultrasound was performed to both locate the implant and measure the thickness of the endometrium according to Fleischer and Kepple.[11]

To measure the effect of FibroPlant-LNG IUS on bleeding patterns, women were questioned during each follow-up visit about the amount of menstrual bleeding and the occurrence of spotting. The following categories were used: no change,half of the original amount of bleeding; a quarter of the original amount of bleeding; scanty menstrual bleedings (panty-liner-type bleeding); irregular spotting; no spotting; amenorrhea. The purpose of this simple evaluation was to obtain an initial clinical impression of the effect of the FibroPlant-LNG IUS on the the amount of bleeding and the presence/absence of continuous or intermittent spotting or amenorrhea.

RESULTS

Between April 1997 and June 2000, a total of 210 FibroPlant-LNG implant systems were inserted for various indications: Hormonal replacement therapy in symptomatic perimenopausal and postmenopausal women, whether or not in combination with estrogen replacement (N=144), treatment of menorrhagia (N=36), treatment of tamoxifen induced uterine bleeding and postmenopausal bleeding (N=11), dysmenorrhea (N=11), contraception (N=80) or any combination of the above.
Eighty women received FibroPlant-LNG IUS for contraception of whom 28 were for contraception and treatment of heavy bleeding.
Only the first 54 women who were followed-up for at least 6 months were included in the current analysis. From this group 18 women were fitted with the IUS for contraception and excessive bleeding. Since the number of insertions is small, no statistical analysis was performed. The events were evaluated on an individual basis. Tables 1 and 2 show the characteristics of the group and table 3 the clinical events.

Table 1. Characteristics of the FibroPlant IUS users (N=54): Age distribution

Average Age	40
Lowest Age	16
Highest Age	51
Age < 20	2 (2%)
Age 21-35	6 (11%)
Age > 35	46 (85%)

Table 2. Characteristics of the FibroPlant IUS users (N=54): Gravidity/Parity distribution

	N	%
0	14	26
>0	40	74

Table 3. Events in the first 54 FibroPlant-LNG users

Events	**N**	**%**
Pregnancy	0	0.0
Expulsion	0	0.0
Failed insertion	0	0.0
Removals for		
Medical reasons	2	3.7
Non-medical reasons	1	1.8
Lost to follow-up	0	0.0
Total No of terminations	3	5.5
Continuation of use	51	94.5
Total women-months	464	
Min. women-months	6	
Max. women-months	16	
No of women	54	

All insertions were successful. Fourteen insertions were performed in nulligravid women. By the end of June 2000, the 54 recruited women had at least 6 months follow-up. Twenty-one were followed-up for at least 12 months at the time of this interim analysis. There were no pregnancies and no hormonal side-effects were reported. After an initial short period of spotting, usually less than 3 months but occasionally more, menstrual bleeding was significantly reduced (to less than half in the beginning but mostly less than a quarter compared with the pretreatment level).

In two women, one with fibroids, it took somewhat longer for the menstrual periods to reduce significantly. There was one exception, also in a woman with fibroids. After an initial period of strongly reduced menstruations, heavy menstrual bleeding resumed but not each month. This case will be further investigated.

Twelve women had medium or large uterine fibroids. All of them, except the one woman mentioned above, reported menstrual blood loss which was less than half,but most often less than a quarter, of the pretreatment level usually starting one month following FibroPlant-LNG IUS insertion. No significant reduction in size of the fibroids could be demonstrated neither clinically, nor by ultrasound examination.
Severe dysmenorrhea was present before treatment in five women. This either disappeared or reduced significantly shortly after FibroPlant-LNG IUS insertion.
Two women complained of weight gain of 5 to 6 kg after approximately 4 months after FibroPlant-LNG IUS insertion. They requested removal of the implant. One woman requested removal after five months in order to make pregnancy possible.
No adverse reactions (e.g., pelvic inflammatory disease, perforation) were reported. There were no expulsions and no users reported pain complaints.
Fifty-one women are continuing to use the method.

DISCUSSION

The FibroPlant-LNG IUS, that releases approximately 14 µg of LNG daily, was developed to provide a strictly localised contraceptive effect and thus minimise systemic hormonal side-effects and amenorrhea.
Amenorrhea occurs in up to 20 % of women wearing the Mirena® intrauterine system that releases significantly more LNG per day. Although it can be looked upon as beneficial to health, amenorrhea also leads to discontinuation of the method in a significant number of women as a result of anxiety and cultural non-acceptance.[1,7,12,13] The FibroPlant-LNG IUS, has a simple physical design and low daily release of LNG. Together these provide optimal tolerance, and avoid the incompatibility problems seen with both conventional IUDs and the Mirena T-shaped LNG-IUS.

The results of this preliminary study suggest that the FibroPlant-LNG IUS, releasing 14 µg of LNG per day, is a safe and effective method of suppressing the endometrium. This gives both effective contraception and a significant reduction of the amount of menstrual bleeding. Women needing contraception and complaining of heavy menses will particularly benefit from these findings.

Spotting usually occurs during the first few months following insertion of the FibroPlant-LNG IUS which can be annoying for some women particularly if this is a daily occurrence. This can be minimised by inserting the FibroPlant-LNG IUS during menses or shortly thereafter. Intermittent scanty bleeding or spotting will be more readily acceptable in women who have been well counseled.

The absence of amenorrhea with the FibroPlant-LNG IUS in this study is probably due to the low LNG release rate and the negligible effect on ovarian function.

Uterine fibroids are very common in women over 40 years of age.[14] They can cause a significant reduction in quality of life especially when they are accompanied by heavy bleeding and pain. This was the situation with a number of women in this study.

Until recently, medical treatment of menorrhagia has been disappointing, especially in women with fibroids. Various surgical techniques in the form of endometrial ablation have been developed. The success of these surgical alternatives is currently being evaluated.

Meanwhile menorraghia is a major reason for hysterectomy among fertile women with or without fibroids. An estimated 600,000 hysterectomies are performed annually in Western Europe and the USA.[15] for the diagnosis dysfunctional uterine bleeding.

The effect of intrauterine delivery of levonorgestrel in women with menorrhagia was tested by Lähteenmäki et al. in women scheduled to undergo hysterectomy.[16] Twenty-eight women received the LNG-IUS Mirena® in an attempt to treat the condition.

Two thirds of women concerned cancelled their decision to undergo hysterectomy because the treatment was successful. The median number of days of bleeding decreased from 7 in the first month to 3 in the 6th month and 2 in the 12th month. It was concluded that treatment of menorrhagia with the LNG-delivery system should be considered before hysterectomy is chosen.

The contraceptive effect in the present study could not be thoroughly studied since most of the women were over 35 years of age and, consequently, less fertile. However, no pregnancies occurred even in the women younger than 35 that formed part of the study.

At 14 µg daily the daily intrauterine release of levonorgestrel from the FibroPlant-LNG IUS is 30% lower than that found with the T-shaped LNG-IUS (Mirena®). This may explain the absence of hormonal side-effects such as mood changes, headache, sleepiness, mastalgia, nausea, and hirsutism which are more likely when higher levonorgestrel doses are used..[1]

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 determined. However, this is expected to be limited, if it takes place at all, as no hormonal side-effects have been reported in the study.

Conclusion

Although the average age of women included was 40, this preliminary study suggests that the FibroPlant-LNG IUS is an effective contraceptive. In addition the FibroPlant-LNG IUS demonstrated a high level of effectiveness in reducing bleeding in women with excessive menstrual flow even when medium or large fibroids were present. An effect, however, on the size of the fibroids could not be demonstrated.

Strong endometrial suppression is the principal mechanism explaining both the contraceptive effect and the effect on menstrual blood loss.

The low daily release rate of levonorgestrel from the FibroPlant-LNG IUS results in an absence of hormonal side effects.

The simple design characteristics and revolutionary anchoring system account for minimising the occurrence of complaints of discomfort pain and expulsion. These, together with the low incidence of amenorrhea give an early indication that the new FibroPlant-LNG IUS may offer significant advantages over the 'framed' Nova-T LNG-IUS (Mirena®).

Acknowledgment
The authors greatly acknowledge Nathalie Lacroix for her help with the processing of the FibroPlant-LNG delivery systems.

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FIGURES

Figure 1. The Mirena® LNG IUS (left) and FibroPlant-LNG IUS (right) after insertion in a uterine model.

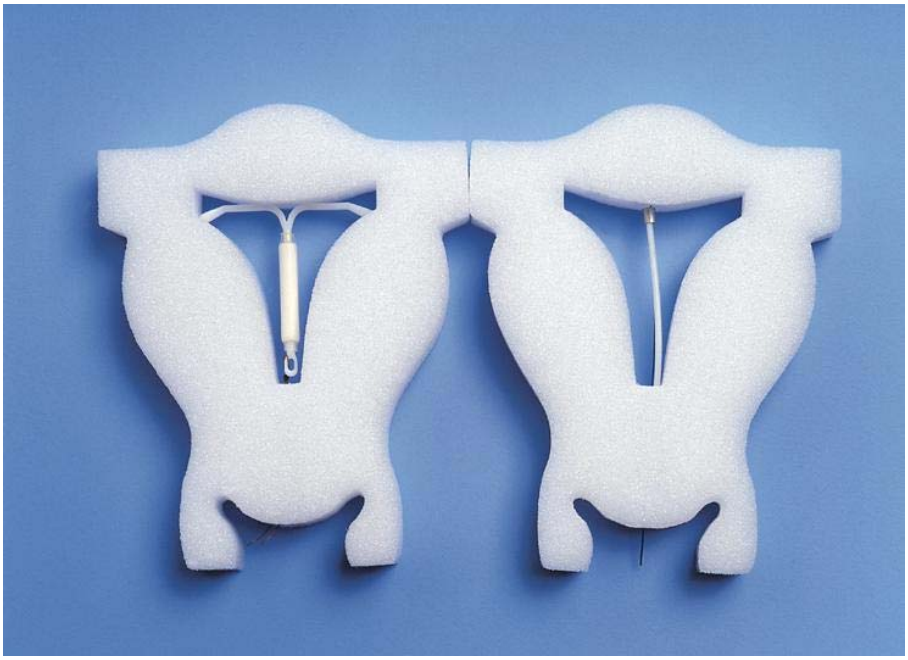

Figure 2. Ultrasound picture of FibroPlant-LNG in situ.

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