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Contraception and treatment in the perimenopause with a novel "frameless" intrauterine levonorgestrel-releasing drug delivery system: an extended pilot study

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Abstract

The objective of the study is 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, in perimenopausal women. An ancillary objective is to evaluate the effect of the new IUS on menstrual blood loss in women with or without fibroids.

The study conducted in one-hundred-nine women suggests that FibroPlant-LNG IUS is an effective contraceptive. No pregnancies occurred with the FibroPlant-LNG IUS. The total use-related discontinuation rate at one year is low (1.9) and results in a high rate of continuation of use (98.1). 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.
Patient satisfaction with the method is high, which is a prerequisite for continuance of the method, and may be linked with the advantageous design charcteristics of the FibroPlant-LNG IUS, the virtual absence of hormonal sideeffects and the low incidence of irregular bleeding and spotting even during the first three months following insertion of the FibroPlant IUS. Counseling remains important though to explain women about the possible occurrence of changes in their menstrual pattern which may sometimes be annoying but harmless.
It is concluded that many women over 40 could substantially benefit from the advantages of this intrauterine drug delivery technology which provides contraception and treatment of a possible associated condition such as menorrhagia. The treatment also creates the opportunity to pass through the transitional perimenopausal period smoothly and to benefit fully from the advantages hormone

replacement therapy offers in terms of treatment of short-term symptoms and long-term prevention by gradually replacing the waning estrogens.

Keywords: : "Frameless" intrauterine system (IUS), Levonorgestrel (LNG), Contraception, Menorrhagia, Hormone Replacement Therapy

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1. Introduction

The perimenopause is the period surrounding the menopause at which time the final menstruation occurs. It is a period of physiological change characterized by a decline in ovarian function and the appearance of symptoms due to deficiency in estrogen/progesterone such as hot flushes, night sweats, depression and sleeping disturbances, which are most disturbing for women. The postmenopause follows the perimenopause and starts 12 months after the last menstrual period [1]. The ovarian function during the perimenopausal phase is not absent as it is mostly in postmenopause [2]. The decline of the hormonal function of the ovary is unpredictable in time and has been estimated to occur approximately 2-8 years before menopause [3,4]. Up to 90% of women may experience menstrual changes during the transition to menopause [5]. Abnormal uterine bleeding is the most frequent gynecological complaint in the perimenopause and the incidence increases as the woman approaches menopause [6,7]. The bleeding is often menorrhagic and is, therefore, an important reason for hysterectomy in the perimenopause [8]. Heavy bleeding is caused by ovulatory dysfunction in approximately half of perimenopausal women as no significant uterine pathology can be found in about 50% of women [9]. Consequently, there is a risk for endometrial hyperplasia and endometrial cancer due to the decline in luteal phase progesterone excretion. Although there is a reduced frequency of ovulation in the perimenopause, contraception is still necessary. Unplanned pregnancies and induced abortions are frequent in women over the age of 40 and are second only to unintented pregnancies in adolescents in the USA [10].

FibroPlant-levonorgestrel (LNG) is a new, "frameless" intrauterine drug delivery system (IUS) which was designed to maintain the advantageous effects of the 20 μg/day LNG-releasing IUS (Mirena®) (Schering AG, Berlin, Germany) whilst addressing reported difficulties in insertion and to reduce troublesome sideeffects such as, disturbed bleeding patterns, amenorrhea and hormonal sideeffects [11]. The FibroPlant-LNG IUS is a further development of the "frameless", copper-bearing GyneFix®

intrauterine contaceptive device (IUD) and 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 elsewhere [12,13]. The FibroPlant-LNG IUS is anchored in the uterine cavity in a similar manner to the "frameless" GyneFix IUD to minimise expulsion. Published statistics show that at least 5% of 'framed' IUD/IUS are expelled during the first year of use [14,15].

The FibroPlant-LNG IUS has been developed in order to provide a pure localized effect on the endometrium to provide a strong contraceptive effect without disturbing the ovarian function. The localized activity of LNG is many times stronger than the effect obtained following oral treatment. This enhanced activity could also be useful for the intrauterine treatment of menorrhagia. The provision of both contraception and treatment is a highly desirable combination in perimenopausal women as 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. Incompatibility problems frequently encountered in perimenopausal women with conventional IUDs and the T-shaped LNG-IUS (Mirena®) are thereby avoided [16,17].

Preliminary clinical studies with the FibroPlant-LNG IUS in peri- and postmenopausal women, releasing 14 μg of LNG per day, suggest that the IUS is effective to provide strong endometrial suppression during estrogen replacement therapy [18]. Clinical trials have also demonstrated the beneficial effect of FibroPlant-LNG IUS in reducing menstrual blood loss, in the treatment of endometrial hyperplasia, and for providing contraception [18-21]. In these studies, the simple design characteristics and anchoring system of the FibroPlant-LNG IUS account for minimizing the occurrence of complaints of pain and expulsion, and the low daily release rate of LNG from the FibroPlant-LNG IUS for the low incidence of hormonal sideeffects.

The main objective of this paper is to report on the use of FibroPlant-LNG IUS in perimenopausal women for contraceptive purposes and for establishing a smooth transition to menopause and replacement of the waning ovarian hormones. In a few women, FibroPlant was used to treat heavy bleeding in addition to the provision of contraception.

2. Materials and methods

2.1. Description of the IUD (Fig. 1)

The FibroPlant-LNG IUS uses the standard GyneFix® anchoring system but has no copper tubes attached to the thread. The copper tubes have been replaced by a 4-cm long and 1.2-mm wide fibrous delivery system, consisting of a LNG-ethylene vinyl acetate (EVA) core and an EVA rate-controlling membrane, 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 five years.

The fibrous delivery system was developed in collaboration with the Polymer Research Group, Department of Chemistry, University of Ghent, Ghent, Belgium. The research was funded by Contrel Research.

2..2 Insertion technique (Fig. 2)

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 technique, thus permanently securing the implant in the uterine cavity.

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 (Fig. 3).

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.

2.3. Admission procedure

Written informed consent was obtained from patients and the Ethics Committee of the Ghent University, Belgium approved the study. Perimenopausal women with climacteric complaints and/or irregular or excessive menstrual bleeding were recruited from the outpatient clinic. 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 routine 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: any 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 and/or undiagnosed genital tract bleeding; known or suspected uterine or cervical malignancy including unresolved, abnormal Pap smear; 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.

The uterine status was evaluated by transvaginal or abdominal ultrasound examination prior to insertion of the implant system. Fibroids were classified clinically and ultrasonographically as follows:

Type I : single or multiple small intramural and subserosal fibroids (< 3 cm). No evidence of submucosal fibroids.

Type II : single or multiple intramural and subserosal fibroids (3-6 cm). No evidence of submucosal fibroids.

Type III : single or multiple intramural and subserosal fibroids (> 6 cm). No evidence of submucosal fibroids.

Subjects with fibroids larger than the size of the uterus at 12 weeks gestation were not admitted in the study. Most fibroids were subserosal or intramural (Fig. 4).

All insertions were performed by the same investigator (DW) and were done without or with local, intracervical, anaesthesia. Following insertion, gentle traction on the tail of the IUS was exerted to feel if the anchor was properly fixed. A transvaginal ultrasound (TVU) was performed (Ultramark® 4Plus, ATL Inc., Bothell, WA, USA) to locate the device in the uterus as described previously [12]. To minimize the drop-out rate, great attention was given to the volunteers to explain the advantages and possible disadvantages of the hormone replacement therapy. Women were told that they could expect scanty intermenstrual bleeding during the first weeks or months but that this is a normal sideeffect which usually disappears in time and should not worry them.

The majority of women received estrogen replacement therapy (ERT) in the form of percutanuous estradiol gel at a continuous dosage of 1.5 mg daily, immediately or later depending on the presence of climacteric symptoms. Some women received a lower dosage (0.75 mg/day) according to their needs as they still had residual ovarian function. A minority of women were treated with transdermal estradiol administration using matrix systems, in a dosage of 50 μg per day.

2.4. Follow-up procedures

Women were followed-up at 1, 3, 6, and 12 months following insertion of the FibroPlant-LNG IUS and six-monthly thereafter. During follow-up the subjects were interviewed about their bleeding patterns and any sideeffects or adverse reactions. On each occasion a full gynecological examination including vaginal ultrasound was performed to both locate the implant, to measure the thickness of the endometrium according to Fleischer and Kepple [22], or to detect any other changes.

To measure the effect of FibroPlant-LNG IUS on bleeding patterns, the following categories were used: no change; half of the original amount of bleeding; a third of the original amount of bleeding; a quarter of the original amount of bleeding; scanty menstrual bleedings (pantyliner-type bleeding); irregular bleeding/spotting; no spotting; amenorrhea.

2.5. Data collection, monitoring and analysis

Data were recorded on standard pre-coded forms at admission, at each scheduled and unscheduled follow-up visit, and upon discontinuation from the study. The cut-off date was 15 July 2001. All data were sent to the data coordinating center at the Department of Medical Informatics and Statistics, University Hospital Gent, Belgium, which provided statistical data analysis for the study. The rates of discontinuation for individual reasons and groups of reasons were analysed using the S-PLUS statistical software package (Mathsoft Corporation) [23] and the cumulative discontinuation rates were computed using survival analysis methods [24,25].

3. Results

3.1. Events at insertion

One-hundred-nine insertions were performed. No insertion failures occurred. There were neither perforations nor PID cases reported immediately following insertion and during the entire follow-up period.

3.2. Subject characteristics

The characteristics of the users are shown in Table 1. The average age of the subjects in the group was 47.1 (range 34 - 55). Eighteen (16.5%) subjects were nulliparous. Fourteen women complained of heavy bleeding. Eleven of them had significant, mostly multiple, fibroids graded as Type III.

3.3. Life table rates

The events and one-year cumulative gross discontinuation rates are presented in Table 2. No pregnancies occurred with the FibroPlant-LNG IUS. The total use-related discontinuation rate at one year is low (1.9) and results in a high rate of continuation of use (98.1) There were five removals for

medical reasons and one for non-medical reasons. One women with excessive and irregular bleeding had an initial positive response which resulted in reduced bleeding. However, the condition worsened and a large endometrial polyp had to be removed by hysteroscopy. A tubal sterilization was performed during the same intervention. Two subjects complained of weight gain and requested removal of the implant, although they developed scanty menstruations with no spotting. The third and fourth removals were in women with irregular bleeding which did not disappear after several months. One subject had ambivalent feelings about "hormones" and requested removal. This subject had small fibroids and quite heavy menstrual periods which greatly reduced during the treatment. After removal of the IUS, the heavy period resumed and the subject is currently considering a new IUS.

Their was a significant reduction of bleeding in all women complaining of excessive bleeding, except the one case with a large endometrial polyp mentioned above. , During interviewing women reported a reduction of at least by half but mostly by three-quartersof the initial amount of blood loss. One subject was treated for simple glandulocystic hyperplasia and developed amenorrhea very quickly after the start of the treatment.
No complications (i.e., perforations, PID) were encountered during this study. The study was well followed-up as only one women did not return for examination and could not be contacted.

4. Discussion

The number of women entering the perimenopause has been growing fast over the last decades. Figures in the US show that there are, at present, nearly 22 million US women in the perimenopausal age group [26]. Although about half of them have undergone tubal sterilization, most of the remaining women in this age group are fertile and still need contraception [27]. Birth rates among women aged 35 years and over have increased significantly over the past decade as women tend to delay pregnancy until later in life. However, about half of them are unplanned and the majority end in induced abortion [10].
For these reasons, there is a need for safe, effective and reversible methods of contraception. This is expressed in a recently published overview article of birth control methods with special reference to the perimenopause [28].

The method often used in many countries is tubal sterilization. In US women aged 40 to 44, half of them rely on this method for birth control but half of the sterilized women would have choosen an effective non-surgical contraceptive method if the option would have been available [29]. Failures rates are few but a recent review reported that the overall cumulative failure rate was 1.9%, most of the failures occurring with the spring clip method [30]. One-third of these pregnancies were ectopic.

Combined oral contraceptives (OCs) are used increasingly by perimenopausal women. However, the proportion of them using OCs is still very small compared with younger age groups. There are several non-contraceptive health benefits of OCs such as the reduction in ovarian and endometrial cancer but there are some concerns about safety. There is a small increased risk of breast cancer in current and past users within the past 10 years. The causal relationship with cervical cancer is still not clear. No increased risk of myocardial infarction and stroke could be found but a small minority of women develop eleveated blood pressure and there is a three- to four-fold increased risk of deep venous thromboembolism.

Intrauterine copper-releasing IUDs are an attractive option for many perimenopausal women with no menstrual disturbances and absence of uterine anomalies. The modern high-load "framed" copper IUDs (e.g., TCu380A and MLCu375) provide high contraceptive efficacy with a five-year cumulative pregnancy rate similar to tubal sterilization. They are extremely safe, long-acting and cost-effective. Recent evidence has shown that the risk of pelvic inflammatory disease is very low [31,32]. Another benefit of IUD use may be the reduction in endometrial and cervical cancer risk [33]. IUDs, however, are underused in many countries, including in the US, but this may change with the development of improved designs and intrauterine drug delivery systems.. The challenge with the development of the frameless GyneFix IUD was to enhance the performance and acceptability of the method. With this new concept, a plastic frame to retain the IUD becomes superfluous, thus overcoming possible dimensional problems responsible for the occurrence of incompatibility problems and sideeffects (e.g., bleeding/pain)

Copper IUDs provide effective contraception but are not suitable for the treatment of menstrual problems. The recently approved levonorgestrel-releasing intrauterine system (LNG IUS), Mirena®, by the USFDA, releasing 20 μg of LNG per day, is a highly effective contraceptive option [11]. In addition to the contraceptive effect, target delivery of LNG has the advantage to reduce menstrual bleeding and to provide endometrial suppression during ERT [34]. However, with the high dose 20 μg-releasing IUS, hormonal sideeffects (e.g., acne, breast tenderness, depression, headache, weight gain) are sometimes a nuisance which often results in discontinuation of the method [35]. Furthermore, insertion difficulties and abdominal pain complaints during the use of the LNG IUS have been reported, especially in perimenopausal women [35,36]. It was suggested, therefore, that low dose intrauterine release of LNG could be sufficient to establish effective contraception and endometrial suppression. LNG provides a strong endometrial suppressive effect which is much higher during intrauterine LNG-delivery than during oral administration of LNG [37]. Recent studies with a 5 μg- and 10 μg-releasing IUS suggested that hormonal side-effects could be avoided without reducing the effectiveness on the endometrium [38].

The results of this study suggest that the FibroPlant-LNG IUS is a safe and effective contraceptive method and an effective method to reduce menstrual bleeding. The study confirms the results obtained in previous studies conducted to assess the effect on menstrual blood loss in women with normal uteri and with fibromyomas [20,21]. Until recently, medical treatment of menorrhagia has been disappointing, especially in women with fibroids. Uterine fibroids are very common in women over 40 years of age. 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. Women needing contraception and complaining of heavy menses will particularly benefit from these findings and, in many cases, hysterectomy could be avoided [39].
Of considerable advantage is that the method gives the woman the opportunity to benefit fully from the seamless replacement of the function of the ovaries at a time when she could be most vulnerable to physical and mental distress due to her changing hormonal situation. As done in this study, estrogens were added when the woman developed climacteric symptoms..

One of the major drawbacks of intrauterine LNGdelivery is the occurrence of irregular bleeding and spotting. 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. However, in the present study, the occurrence of spotting was low and only a few removals were done for that reason, which may be due to the low dose of LNG. Most women who continued to have menstrual bleeding had scanty regular menses without spotting. Irregular bleeding and spotting can be minimized by inserting the FibroPlant-LNG IUS during menses. Another way to avoid bleeding disturbances during the initial months following the insertion of the IUS would be to administer a low dose of estrogen from the beginning to induce endometrial tissue repair of the progestogen-induced defects in the overlying endometrium [40]. Intermittent scanty bleeding or spotting will be more readily acceptable in women who have been well counseled. In some women with amenorrhea, the recurrence of slight spotting has been observed. This blood-stained discharge disappears usually within a few days.

In the present study, it appeared that two categories of women could be distinguished based on their endometrial response: 1) perimenopausal women with rapidly declining ovarian function; and 2) perimenopausal women with fluctuating or intermittent ovarian function. Women belonging to the first group seem to develop endometrial atrophy and amenorrhea soon after treatment initiation probably as a consequence of the rapidly declining estrogen level. The second group of perimenopausal women will pass through a transitional phase, with strongly reduced bleeding until amenorrhea occurs as a result of the further waning of ovarian function and the suppressive effect of the LNG. These women appear to be the most vulnerable to irregular and unpredictable bleeding.

5. Conclusion

Many women over 40 could substantially benefit from the advantages of intrauterine drug delivery which provides contraception and treatment of a possible associated condition such as menorrhagia. The treatment also creates the opportunity to pass through the transitional perimenopausal period smoothly and to benefit fully from the advantages hormone replacement therapy offers in terms treatment of short-term symptoms and long-term prevention by gradually replacing the waning estrogens.

The study suggests that 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.

Patient satisfaction with the method is high, which is a prerequisite for continuance of the method, and may be linked with the advantageous design characteristics the FibroPlant-LNG IUS, the virtual absence of hormonal side effects and the low incidence of irregular bleeding and spotting even during the first three months following insertion of the FibroPlant IUS. Counseling remains important though to explain to women about the possible occurrence of changes in their menstrual pattern which may sometimes be annoying but harmless.

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FIGURES

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

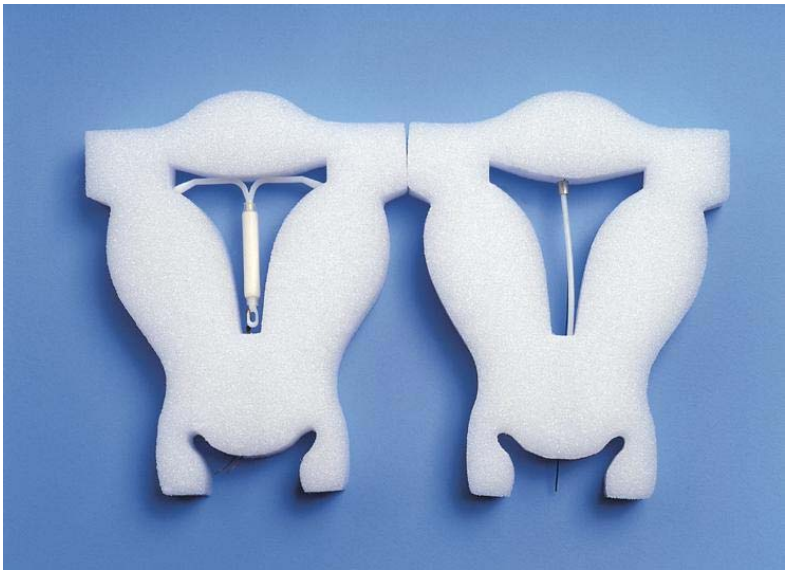


Fig. 2. Insertion procedure of the FibroPlant-LNG IUS: Step 1) insertion of the instrument up to the uterine fundus; Step 2) anchoring of the device by pushing the inserter forward slowly and gently; Step 3) removal of the inserter.

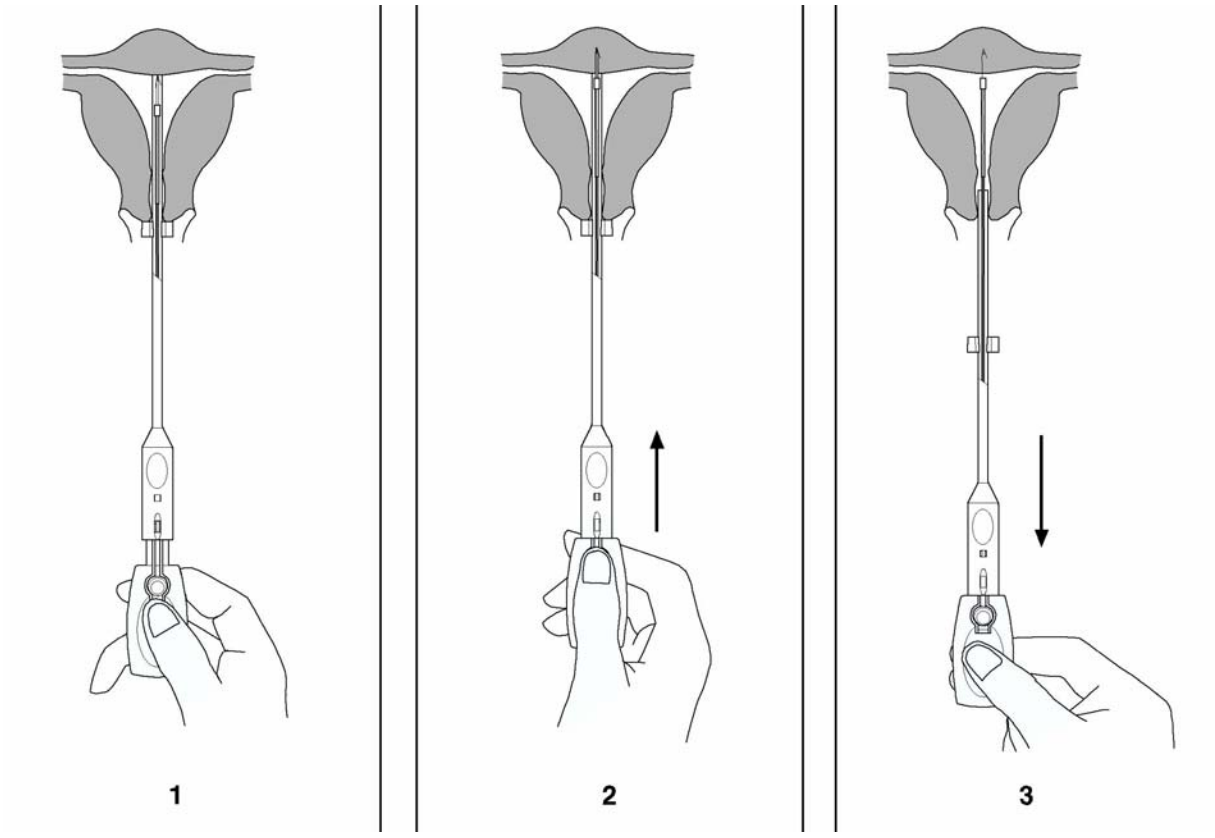
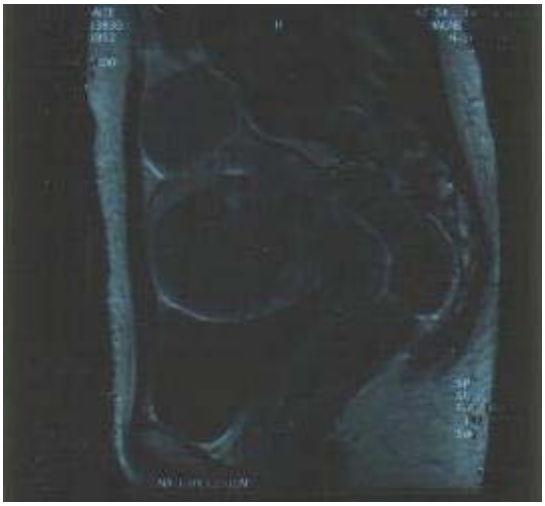


Fig. 3. Ultrasound picture of FibroPlant-LNG IUS in situ.

Fig. 4. MRI in a patient with multiple uterine fibroids (largest 7.5 cm in diameter) responding very well to intrauterine treatment with LNG. In the center of the uterus, the FibroPlant-LNG IUS is clearly visible (clear line-shaped zone).



TABLES

Table 1. Characteristics of the FibroPlant-LNG IUS users

n = 109	Age (years)	Gravidity	Parity
Mean	47.1	1.4	1.4
SD	3.6	0.9	0.9
Min	39	0	0
Max	55	3	3

Table 2. Events and cumulative gross discontinuation rates per 100 women using the FibroPlant-LNG

	No.	Rate ± SD
Pregnancy	0	0
Expulsion	0	0
Removal for medical reasons	5	1.9 (0, 4.5)
Removal for non- medical reasons	1	0
Removal for 'other reasons'	0	0
Total use-related discontinuation	6	1.9 (0, 4.5)
Loss to follow-up	1	1 (0, 2.9)
Continuation	103	98.1 (95.5, 100)
Women recruited	109	
Women-months of use (one year)	1064	

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