

Treatment of primary and secondary dysmenorrhea with a novel “frameless” intrauterine levonorgestrel-releasing drug delivery system: a pilot study

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ABSTRACT

Objective To evaluate the effect on menstrual pain in women with primary and secondary dysmenorrhea 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. Eighteen insertions were performed in women between 16 and 52 years of age by the first author. Four insertions were done in nulligravid women. Eight women were categorized as having primary dysmenorrhea and 12 as having secondary dysmenorrhea. Twelve women complained of heavy bleeding. Three women had significant fibroids and 3 were suspected to have adenomyosis.

Results The trial covers a period from a minimum of 3 months up to 33 months. By the end of August 2001, 12 recruited women had at least 12 months follow-up and 6 between 3 months and one year. All women reported much reduced pain, or no pain at all, and strongly reduced bleeding which started as soon as one month after insertion of the FibroPlant-LNG IUS. There was one exception. The latter woman had significant fibroids. She reported much reduced bleeding but this was not as pronounced as in the other women in the study. All women are continuing to use the method.

Conclusion 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 for the treatment of primary and secondary dysmenorrhea. The absence of a frame is particularly advantageous in these

women. Of significant added importance of this LNG IUS is its high effectiveness in reducing menstrual bleeding, a symptom often present in women with menstrual pain complaints, and the fact that the system provides effective contraception. The low daily release rate of levonorgestrel from the FibroPlant-LNG IUS results in a virtual absence of hormonal side effects.

KEY WORDS: “Frameless” intrauterine system (IUS), levonorgestrel (LNG), dysmenorrhea, heavy bleeding, contraception, pilot study

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INTRODUCTION

Dysmenorrhea is described as a very common gynecological problem. In articles about the subject, it is mentioned that dysmenorrhea is typical in young, nulliparous women. About 50 per cent of them suffer from pain during menstruation and some 10-20 per cent are absent from work for 1 or 2 days each or every second menstruation.^{1,2} Studies have also shown that dysmenorrhea improves or disappears after the first birth but, also that menstrual pain is not uncommon in older women. As high as 30 per cent of 30-40 year old women still complain of menstrual pain.¹

Primary or spasmodic dysmenorrhea should be distinguished from secondary dysmenorrhea. In primary dysmenorrhea, the underlying basis is myometrial hyperactivity which causes local hypoxia due to an increased local secretion of vasopressin and prostaglandins. These hormones have a profound effect not only on the myometrium but also on the smooth muscle of the arterial walls. The causes of secondary dysmenorrhea are diverse: intrauterine pathology (e.g., fibroids, adenomyosis, polyps, the presence of an intrauterine device); extrauterine pathology (e.g., endometriosis, pelvic inflammatory disease); and outflow obstructions (e.g., Müllerian duct abnormalities, cervical stenosis).

Many options for both conservative and surgical treatment are available to alleviate primary and secondary dysmenorrhea: non-steroidal anti-inflammatory drugs (NSAIDs), combined oral contraceptives, progesterone, nifedipine, beta adrenoceptor agonists, danazol, gonadotrophin-releasing hormone agonists and the recently developed transcutaneous nerve stimulation

(TENS) method. In addition, division of the utero-sacral ligaments using laser or electrocautery at the time of laparoscopy can be used and presacral neurectomy, which can also be performed laparoscopically, have been used with success in primary dysmenorrhea. For secondary dysmenorrhea, surgery (e.g., hysterectomy, endometrial ablation) can be helpful if medical treatment fails.⁴

It is not surprising that the levonorgestrel (LNG)-releasing T-shaped intrauterine system (IUS), Mirena[®] (Schering AG, Berlin, Germany) has been used successfully in primary and secondary dysmenorrhea since it causes a strong suppressive effect on the endometrium. The therapeutic effect of the system is mediated through the reduction in prostaglandin synthesis in the endometrium.⁵ The LNG IUS was also effective in alleviating dysmenorrhea in the presence of rectovaginal endometriosis which is commonly associated with severe dysmenorrhea, dyspareunia, and pelvic pain.⁶

The FibroPlant-LNG intrauterine system (IUS) used in this study was designed to maintain the advantageous effects of the 20 µg/day T-LNG IUS (Mirena[®]) whilst addressing reported difficulties in insertion and reducing troublesome side effects such as, disturbed bleeding patterns, amenorrhea and hormonal side effects.⁷ The FibroPlant-LNG intrauterine system is a further development of the “frameless”, copper bearing GyneFix[®] intrauterine contraceptive device and uses the same anchoring technology that has been *shown in practice* to be compatible with uterine cavities of virtually all shapes and sizes. The system is anchored in the uterine cavity to minimise expulsion and to avoid the use of a plastic frame. This is important as published statistics show that at least 5% of ‘framed’ IUDs/IUS are expelled during the first year of use.^{8,9}

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 dysmenorrhea and excessive menstrual bleeding. Furthermore, LNG delivered in the uterine cavity provides a strong contraceptive effect. Preliminary clinical studies have shown that Fibroplant-LNG is highly effective in establishing endometrial suppression during ERT, in reducing menstrual blood loss and to provide effective contraception.^{10,12}

The provision of both contraception and treatment is a highly desirable combination in young women who frequently complain of dysmenorrhea. The physical design characteristics of the FibroPlant-LNG IUS provide optimal tolerance and avoid the incompatibility problems frequently encountered with conventional IUDs and the T-shaped LNG-IUS.

The lower release rate of FibroPlant-LNG (14 µg/day) in comparison 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.

This pilot study with a follow-up period of between 3 months and 33 months was conducted primarily to evaluate the performance of the FibroPlant-IUS in primary and secondary dysmenorrhea.

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 studies show that the rate of LNG release is constant over several years (zero-order). The duration of release, calculated by extrapolation, is at least 3 years.

The fibrous delivery system was developed in cooperation 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 (Figure 2). 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

Written informed consent was obtained from patients and the Ethics Committee of the Ghent University, Belgium approved the study.

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: 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; known 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.

Prior to insertion, a full medical history was taken, 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). The regularity of the uterine cavity was checked by transvaginal ultrasound examination (Ultramark[®] 4Plus, ATL Inc., USA) and magnetic resonance imaging was performed, if required, to assess the uterus in more detail.

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. One investigator (DW) performed all insertions. 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.

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 they were questioned about menstrual pain and about their bleeding pattern and any side effects or adverse reactions. On each

occasion a gynecological examination including vaginal ultrasound was performed to verify the position of the IUS and any changes that may have occurred.

RESULTS

Between November 1998 and March 2001, 18 FibroPlant-LNG IUS were inserted to treat heavy bleeding, dysmenorrhea and, in most women, to provide for contraception. Four insertions were performed in nulliparous women. Eight women were categorized as having primary dysmenorrhea as no organic cause for the painful menstrual periods could be found. In twelve women, an anomaly of the uterus was found. Three women had significant multiple intramural or subserosal fibroids as confirmed by ultrasound and magnetic resonance imaging (Figure 3). Two other women had small fibroids and 4 had enlarged uteri without apparent other uterine anomalies. Three women were suspected to have uterine adenomyosis.

In this study, the effect of treatment on pain complaints was assessed by questioning. Menstrual pain was graded as follows: no pain; almost no pain; much reduced pain; no change in pain compared with before. The amount of blood loss was evaluated using a pictorial bleeding chart as described previously.¹² Since the number of insertions is small, no statistical analysis was performed. Tables 1 shows the characteristics of the group and clinical events at the last follow-up visit.

All women in this study reported much reduced pain, or no pain at all, and strongly reduced bleeding which started as soon as one month after insertion of the FibroPlant-LNG IUS. There was one exception. The latter woman had significant fibroids. She reported much reduced bleeding but this was not as pronounced as in the other women in the study. All women are continuing to use the method.

DISCUSSION

In women with primary dysmenorrhea, the concentrations of prostaglandins (PG), both $\text{PGF}_{2\alpha}$ and PGE_2 , in menstrual blood are significantly increased compared to those in women without dysmenorrhea as a result of endometrial synthesis and release of PGs.^{13,14} It is, therefore, logical that in the clinical management of both primary and secondary dysmenorrhea, non-steroidal anti-inflammatory drugs which inhibit PG synthesis offer a valid treatment. However, the treatment is less effective if the intake of the drug is delayed until the

pain is more severe. Also side effects can occur especially in women with asthma and allergic disorders, and those with peptic ulceration.¹⁵

Oral contraceptives are still used very often to treat dysmenorrhea especially in young women who also require contraception. The pill reduces uterine contractility, induces endometrial atrophy and reduces endometrial PG concentrations. However, the side effects and potential of adverse drug reactions may limit their use in some women.

Other treatments have either too many side-effects (e.g., danazol, gonadotrophin-releasing hormone agonists), are too invasive (e.g., surgical methods), or are ineffective for the treatment of an accompanying disorder, and cannot, therefore, be considered for routine treatment of dysmenorrhea.

FibroPlant-LNG IUS, that releases approximately 14 µg of LNG daily, was developed to provide a strictly localised effect on the endometrium to treat various gynecological disorders, and to provide contraception. The released dose was reduced to minimise systemic hormonal side effects and amenorrhea.

In previous studies, the "frameless" intrauterine LNG-releasing system was evaluated for the treatment of menorrhagia, endometrial hyperplasia, and for endometrial suppression during estrogen replacement therapy.¹⁰⁻¹² These studies demonstrated that the FibroPlant-LNG system is effective to suppress the endometrium and to treat these disorders.

The present study suggests that the FibroPlant-LNG IUS is highly effective in primary as well as secondary dysmenorrhea. The treatment works through continuous inhibition of PG synthesis and by establishing endometrial atrophy which results in a marked decrease in menstrual pain and blood loss. In this small series of 18 women, 8 women were categorized as having primary dysmenorrhea, and 10 as secondary dysmenorrhea. Reduction or total absence of menstrual pain and strong reduction of bleeding occurred in the two categories of women, including in those women with significant fibroids and heavy bleeding.

Leiomyomata are often asymptomatic but some 25-50% of women will experience symptoms such as menorrhagia and pelvic discomfort. About 5% of the fibroids are intracavitary and submucosal and are most difficult to treat.^{16,17}

The percentage of women with menorrhagia is significantly higher above 40 years of age.¹⁸ This is mainly explained by the higher frequency of uterine pathology, such as fibroids and polyps, which are more common during the premenopausal years. However, in 50% of women with menorrhagia, no gross pathology can be demonstrated.¹⁹ This seems to be

confirmed in the present study. Local defects in the haemostatic mechanism in the endometrium are most probably at the origin of the disorder such as an increased fibrinolytic activity or an imbalance in the different types of prostaglandins.²⁰

The frameless design of the FibroPlant-LNG IUS avoids the incompatibility problems seen with both conventional IUDs and the Mirena T-shaped LNG-IUS. This is a significant advantage especially in women with dysmenorrhea who may also have a distorted uterine cavity as may be the case in the presence of fibroids.

Conclusion

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 for the treatment of primary and secondary dysmenorrhea. The absence of a frame is particularly advantageous in these women. Of significant added importance of this LNG IUS is its high effectiveness to treat excessive menstrual bleeding, a symptom often present in women with menstrual pain complaints, and the fact that the system provides effective contraception. The low daily release rate of levonorgestrel from the FibroPlant-LNG IUS results in a virtual absence of hormonal side effects.

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FIGURES

Figure 1. The FibroPlant-LNG intrauterine system after insertion in a uterine model.



Figure 2. Ultrasound picture with FibroPlant-LNG in situ. In this case, the S-S distance (= distance from the serosal surface to the stainless steel clip) is 14 mm.



Figure 3. MRI in patient n° 16 with multiple uterine fibroids (largest 3 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 study group and events in 18 FibroPlant-LNG users.

No	DATE OF BIRTH (yymmdd)	INDICATION	INSERTION DATE	LAST FOLLOW-UP AND COMMENTS
1.	55 08 20	<ul style="list-style-type: none"> • Primary dysmenorrhea • Heavy bleeding 	13-11-98	<ul style="list-style-type: none"> • Last visit 04-04-01: almost complete absence of pain; scanty menstrual bleeding
2.	55 11 27	<ul style="list-style-type: none"> • Primary dysmenorrhea • Heavy bleeding 	20-01-99	<ul style="list-style-type: none"> • Last visit 07-02-01: no pain; scanty menstrual bleeding
3.	57 05 15	<ul style="list-style-type: none"> • Secondary dysmenorrhea • Heavy bleeding • Suspicion of adenomyosis 	25-02-99	<ul style="list-style-type: none"> • Last visit 18-06-01: much reduced pain and bleeding
4.	56 10 08	<ul style="list-style-type: none"> • Secondary dysmenorrhea • Heavy bleeding • Presence of significant fibroids 	12-03-99	<ul style="list-style-type: none"> • Last visit 05-05-01: much reduced pain and bleeding
5.	54 04 28	<ul style="list-style-type: none"> • Secondary dysmenorrhea • Heavy bleeding • Presence of small fibroids 	23-03-99	<ul style="list-style-type: none"> • Last visit 09-01-01: no pain; much reduced bleeding
6.	49 12 15	<ul style="list-style-type: none"> • Secondary dysmenorrhea • Heavy bleeding 	30-04-99	<ul style="list-style-type: none"> • Last visit 01-08-01: no pain; amenorrhea
7.	80 08 07	<ul style="list-style-type: none"> • Primary dysmenorrhea • Oligomenorrhea 	08-05-99	<ul style="list-style-type: none"> • Last visit 06-01-01: no pain; almost total absence of bleeding
8.	52 10 08	<ul style="list-style-type: none"> • Primary dysmenorrhea • Heavy bleeding 	01-10-99	<ul style="list-style-type: none"> • Last visit 02-04-01: no pain; scanty menstrual bleeding
9.	83 09 28	<ul style="list-style-type: none"> • Primary dysmenorrhea • Normal menstruations 	29-11-99	<ul style="list-style-type: none"> • Last visit 13-03-01: no pain; scanty menstrual bleeding
10.	57 05 26	<ul style="list-style-type: none"> • Secondary dysmenorrhea • Heavy bleeding • Suspicion of adenomyosis 	24-01-00	<ul style="list-style-type: none"> • Last visit 02-04-01: no pain; scanty menstrual bleeding
11.	65 03 23	<ul style="list-style-type: none"> • Secondary dysmenorrhea • Heavy bleeding • Presence of significant fibroids 	10-02-00	<ul style="list-style-type: none"> • Last visit 10-03-01: no pain; scanty menstrual bleeding
12.	60 12 25	<ul style="list-style-type: none"> • Primary dysmenorrhea • Heavy bleeding 	14-03-00	<ul style="list-style-type: none"> • Last visit 09-05-01: much reduced pain; scanty menstrual bleeding
13.	51 03 12	<ul style="list-style-type: none"> • Secondary dysmenorrhea • Heavy bleeding • Presence of small fibroids 	19-06-00	<ul style="list-style-type: none"> • Last visit 02-04-01: no pain; much reduced bleeding
14.	69 01 23	<ul style="list-style-type: none"> • Primary dysmenorrhea • Normal menstruations 	19-06-00	<ul style="list-style-type: none"> • Last visit 07-05-01: no pain; much reduced bleeding
15.	51 10 11	<ul style="list-style-type: none"> • Primary dysmenorrhea • Normal menstruations 	03-07-00	<ul style="list-style-type: none"> • Last visit 20-06-01: no pain; much reduced bleeding
16.	48 08 02	<ul style="list-style-type: none"> • Secondary dysmenorrhea • Presence of significant fibroids 	28-09-00	<ul style="list-style-type: none"> • Last visit 20-06-01: no pain; much reduced bleeding
17.	55 08 25	<ul style="list-style-type: none"> • Secondary dysmenorrhea • Heavy bleeding • Suspicion of adenomyosis 	31-10-00	<ul style="list-style-type: none"> • Last visit 13-03-01: much reduced pain and bleeding
18.	84 08 13	<ul style="list-style-type: none"> • Primary dysmenorrhea • Normal menstruations 	27-03-01	<ul style="list-style-type: none"> • Last visit 26-06-01: much reduced pain and bleeding

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