

Reviews

Development of a miniature, low-dose, frameless intrauterine levonorgestrel-releasing system for contraception and treatment: a review of initial clinical experience



Dr Dirk Wildemeersch

Dr Wildemeersch (1944) is the inventor of the 'frameless' IUD, GyneFix, and developer of the GynePlant and FibroPlant intrauterine drug delivery systems. He completed his medical training at the University of Ghent, Belgium, and graduated in gynaecology in 1976. His research and development activities started in 1985, after 10 years of busy gynaecological and obstetrical practice. Since then, he has devoted considerable time to the clinical development of new IUD concepts and implant systems, originally in collaboration with a group of gynaecologists working at the University of Ghent, Belgium. Under Dr Wildemeersch' supervision, a research company, *Contrel*, was established to manage clinical research and to continue to develop and study innovative drug delivery technologies. He has acquired substantial expertise in IUD research and controlled release of bioactive drug substances. His main topics of interest are contraception, and intrauterine drug delivery for the treatment of menorrhagia and other gynaecological conditions including postmenopausal treatment. Dr Wildemeersch remains devoted to his patients in his gynaecological practice in Knokke, Belgium, and is an active member of the European Society of Contraception and other scientific organizations.

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Abstract

A low-dose levonorgestrel (LNG)-releasing intrauterine system (IUS) (FibroPlant) has been clinically developed since 1997 for endometrial suppression during hormone replacement therapy in peri- and postmenopausal women, for the treatment of menorrhagia in women with normal uteri or with uterine fibroids, for contraception, for the treatment of endometrial hyperplasia, and for alleviating primary and secondary dysmenorrhoea. Results of preliminary studies confirm the promising nature of this all-round drug delivery system. The low dose of LNG released accounts for the low hormonal side-effect rate and virtual absence of amenorrhoea in premenopausal women. The system has not yet been evaluated in tamoxifen users (to protect the endometrium), or in women with rectovaginal endometriosis. However, early indications suggest that the system will also be suitable for these indications. The frameless drug delivery support of this LNG-releasing IUS has been optimized to reduce the size of the foreign body and to maximize tolerance and continuation of use while simultaneously providing for the maximum duration of action.

Keywords: contraception, intrauterine drug delivery, levonorgestrel, treatment

Introduction

Quality of life issues are extremely important when it comes to correct and consistent use of contraceptives. Combined oral contraceptives (OC) are still used frequently in Western countries, despite concern by women about the effect of daily

intake on their health. Nuisance side-effects are common and are the main reason for discontinuation, predisposing to unintended pregnancy. In the USA, the typical failure rate of OC is 5% per year (Trussell, 1999). The leading birth control method in the USA, UK, and in other major developed as well as developing countries such as India and China, is tubal

Declared interest: Dirk Wildemeersch is Medical Director of Contrel Research, a company which was established to manage clinical research and to develop and study innovative drug delivery technologies aimed at finding improved methods for prevention and treatment of gynaecological conditions, improvements to birth control methods and higher levels of safety, user acceptability, compliance and quality of life for women. Contrel is the manufacturer of GyneFix and FibroPlant. The funds generated are re-invested in research.

sterilization. Tubal sterilization is irreversible and many women would have selected another method, if they were offered an alternative. Consequently, there is a need for alternative birth control methods which are not dependent on daily administration and which reduce side-effects, and are therefore more acceptable.

New developments in the field of intrauterine contraception and drug delivery possess the attributes to provide both effective contraception and treatment.

The most common side-effects of 'framed' intrauterine devices (IUD) are bleeding and pain. The prevalence of complaints of bleeding and pain vary according to both the patient and the IUD used. In general, the greater the surface area and size of an IUD, the higher the incidence of removal for bleeding and pain. Young nulliparous women and those with low parity are particularly prone to report bleeding and pain. Disproportion between the IUD and the uterine cavity results from an IUD with a fixed shape and size that is inserted in a cavity that varies in shape and size in each woman. Even in the same woman, the uterine cavity changes slightly during the various phases of the menstrual cycle.

The frameless and anchored IUD was developed in 1985 (Wildemeersch *et al.*, 1988). Six copper tubes are fixed on a length of suture thread (**Figure 1**). The proximal end is provided with a knot, which is implanted in the myometrium with an inserter to secure the IUD permanently in the uterine cavity. With this new concept, dimensional problems are avoided. In 1995, a mini GyneFix IUD was developed which has only four copper tubes attached to the anchoring thread. Its small surface area, however, is one-third smaller than that of the regular GyneFix IUD, one-third of the surface area of that of the TCu380 IUD and one-sixth of that of the Lippes Loop.

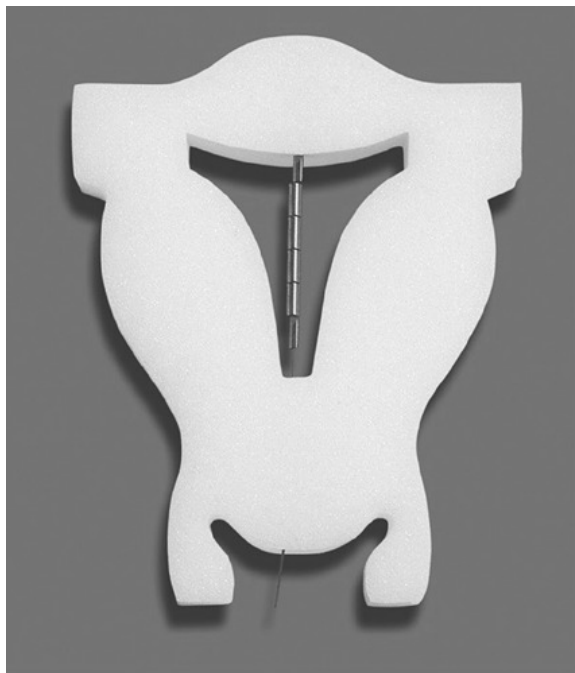


Figure 1. The GyneFix standard IUD.

A reduced effect on bleeding patterns can therefore be expected as the mini GyneFix device is so much smaller. The magnitude of the increase in menstrual bleeding is related to the size of the device. With larger types of non-medicated IUD, i.e. Lippes Loop, the blood loss is ~70–80 ml, approximately double that of the normal menstrual flow. The amount of excess bleeding is less (50–60 ml) with the smaller 'framed' copper devices. This amount is likely to be even less with the GyneFix mini IUD as this device has a significantly smaller surface area.

Figure 2 shows the progress made over the years since the 1960s as regards the surface area of the IUD. It can be expected that not only the effect on menstrual blood loss, but also complaints of pain, expulsion and the occurrence of accidental pregnancy, are to a certain extent governed by the physical size of the older generation IUD which can overdistend or place pressure upon the uterine cavity, resulting in uterine cramping and partial or total propulsion of the foreign body from the uterine cavity. Incomplete expulsion greatly reduces contraceptive efficacy.

The frameless IUD, although adding important new dimensions to intrauterine contraception in terms of performance and patient acceptability, does not by itself reduce bleeding. This can be achieved by delivering intrauterine progestogens. Dr Tapani Luukkainen, the inventor of the Nova-T IUD (a copper-T device with flexible arms), initiated his search for a long-acting steroid-medicated IUD in the early 1970s. The T-LNG emerged in 1976, a Nova-T from which the copper filament had been removed and the vertical arm replaced by a small reservoir releasing a daily dose of levonorgestrel (LNG) for at least 5 years. The commercial name of this device is Mirena® (Leiras-Schering) and it is the first and so far only serviceable steroid-containing IUD that is



Figure 2. Three generations of IUD (left to right), Lippes Loop (1960), TCu380A (1980), GyneFix-mini (2000).

commercially available. Its clinical effectiveness, resulting from atrophy of the endometrium and the physicochemical changes of the cervical mucus produced by the progestogen, is comparable with that of the combined Pill when this is used correctly. The mucus plug acts as a barrier to both sperm cells and bacteria, hence the low incidence of PID, although this has not been confirmed in all studies. The main drawbacks of the Mirena[®] are that it produces amenorrhoea, troublesome hormonal side-effects and disturbed bleeding patterns which may be a problem for some wearers in certain societies for cultural reasons (Sturridge and Guillebaud, 1996; Thiery, 1997; Cox and Blacksell, 2000).

The 'frameless' LNG intrauterine system (IUS) has been developed from the frameless copper IUD (GyneFix[®]) and consists of two components, a 4 cm long coaxial fibrous delivery system, which delivers 14 µg/day of LNG for a period of 5 years, and the conventional anchoring system used with the frameless GyneFix[®] IUD. The fibrous delivery system is attached to the anchoring system by means of a metal clip at the upper end of the fibre that is visible on ultrasound, to allow proper location of the system in the uterine cavity. The two-component system is extremely simple and women-friendly, adapting to cavities of every size and shape. This is one of the main advantages of this new intrauterine LNG-delivery system. **Figure 3** shows the FibroPlant-LNG IUS compared with the T-LNG IUS (Mirena[®]) and **Figure 4** a transvaginal ultrasound scan of the IUS *in situ*.

The purpose of this paper is to review the clinical results, both published and unpublished, with the frameless FibroPlant-LNG IUS for contraception and the treatment of gynaecological conditions such as menorrhagia, dysmenorrhoea, endometrial hyperplasia and for endometrial suppression during oestrogen replacement therapy in peri- and postmenopausal women. Our intention in this paper is to show that targeted delivery of LNG is preferable to other routes of administering a drug.

Clinical results obtained in various disorders with a miniature low-dose levonorgestrel intrauterine system

Hormone replacement therapy (HRT)

Climacteric symptoms are most distressing during the perimenopausal and early postmenopausal years. The majority of women take HRT to obtain relief from climacteric symptoms rather than for prevention of cardiovascular disease or osteoporosis. It is known that a high number of women will not continue the sustained use of the treatment necessary to derive long-term health benefits. As low as 40% or less of women taking oral HRT will continue it for more than a year (Hammond, 1994; Castelo-Branco *et al.*, 1999; Ettinger *et al.*, 1999; Hill *et al.*, 2000). Reinitiation of bleeding, breakthrough bleeding and hormonal side-effects, caused by systemic progestogen absorption, are usually the reason for discontinuing the therapy. It appears to us, therefore, that optimal patient compliance will only be obtained if these factors are fully dealt with. Women will then be able to receive the full impact of the preventive health benefits of HRT.

With conventional oestrogen-progestogen combinations, sequential or continuous combined regimens, the likelihood of continuous or erratic breakthrough bleeding has been reported to be as high as 64% and is the most important reason to discontinue the method in over 30% of women (Whitehead, 1998).

Continuous combined HRT has been developed to cause amenorrhoea by inducing endometrial atrophy. This treatment regimen has been called 'bleed-free', but for many patients this is not entirely accurate. Higher doses of progestogen might help in reducing these irregular bleedings but this increases side-effects and metabolic consequences due to the higher progestogen concentrations (Magoo *et al.*, 1985). In long-cycle HRT, the frequency of bleeding is reduced because the progestogen is added only every third month. However, one study reported a significant increase in the incidence of simple and complex hyperplasia, and carcinoma (Cerin *et al.*, 1996). The duration of the progestogen administration seems more important than the daily dose as far as prevention of endometrial hyperplasia is concerned (Whitehead *et al.*, 1990). These treatments are therefore unsuitable for many women

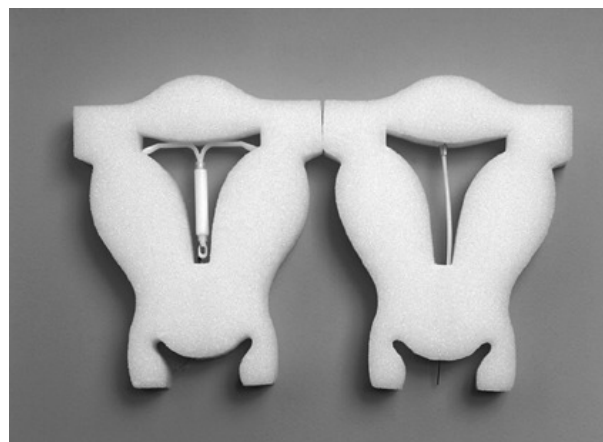


Figure 3. Mirena[®] LNG IUS (left) and the FibroPlant-LNG IUS (right) after insertion in a uterine model.

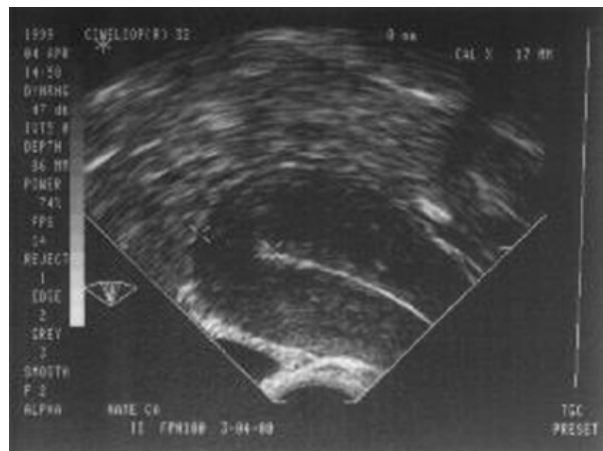


Figure 4. Transvaginal ultrasound scan of the FibroPlant-LNG IUS *in situ*.

during the perimenopause and within 12 months of the last menstrual period (Whitehead, 1998).

Clinical observations

In an earlier study (unpublished data), the 14 µg-releasing FibroPlant-LNG IUS was tested in 82 perimenopausal and 59 postmenopausal women. Over 90% were followed-up for at least 1 year (range 8–21 months). Fifty-one perimenopausal women received the IUS for contraception in addition to oestrogen replacement therapy. Of the total group of 141 women, 108 women maintained or developed amenorrhoea, 52 or 63.5% of the perimenopausal and 100% of the postmenopausal women respectively. Twenty-one perimenopausal women (25.6%) had strongly reduced regular menstruations without spotting. Seven women (8.5%) complained of significant irregular bleeding, which was responsible for three of the four removals in the study. In one of them a large polyp (2.5 cm in diameter) was removed. Eleven women with heavy bleeding (five of them with significant fibroids) were all successfully treated, except one. All women with hyperplasia (six simple and two atypical adenomatous hyperplasia) were treated effectively.

The ultrasonographic appearance of the endometrium was that of endometrial atrophy (<5 mm in thickness) in all amenorrhoeic women as well as in the women who continued to have slight bleeding.

The study confirms previous studies conducted with the T-LNG IUS that showed that continuous exposure to LNG results in a uniform suppression of the endometrium as soon as 1 month after treatment initiation and remains constant during prolonged use (Silverberg *et al.*, 1986). Although the bleeding pattern in the study was not evaluated separately, the low-dose FibroPlant-LNG IUS did not seem to cause significant irregular bleeding or spotting in the majority of women. Only three women with irregular and erratic bleeding requested removal of the IUS. This is in agreement with studies conducted with the T-LNG IUS in perimenopausal women (Boon, 1998).

Patient satisfaction and continuance depends on the presence or absence of bleeding problems. Optimal long-term compliance can be expected if abnormal bleeding can be minimized. The high incidence of amenorrhoea obtained with the low-dose LNG IUS has been advantageous to perimenopausal women. They expect this as a normal occurrence in this phase of their lives. Sixty-three percent of perimenopausal women became amenorrhoeic. This is similar to the 61.7% amenorrhoea rate after 2 years reported in studies with the T-LNG IUS in perimenopausal women (Boon, 1998).

In this FibroPlant-LNG study conducted in peri- and postmenopausal women, women can be categorized into three different groups depending on their endometrial response: (i) postmenopausal women with absent ovarian function; (ii) perimenopausal women with rapidly declining ovarian function; and (iii) perimenopausal women with fluctuating or intermittent ovarian function. The first two groups developed an atrophic endometrium and amenorrhoea soon after treatment initiation, as a consequence of profound endometrial suppression and probably reduced oestrogen

concentrations. The third group of perimenopausal women will pass through a transitional phase, with strongly reduced bleeding until amenorrhoea occurs as a result of the further waning of ovarian function and the suppressive effect of LNG. These women appear to be the most vulnerable to irregular and unpredictable bleeding.

Of importance is the reduced effect of mini quantities of locally administered LNG on lipid metabolism and serum lipoproteins. With the 20 µg/day releasing T-LNG IUS, lipid, lipoprotein and metabolic changes still may occur. The negative influence of LNG is also dose dependent when administered with an intrauterine system. It is therefore imperative to develop low-dose systems that avoid the negative influence on lipid and lipoprotein profiles, to maximize the cardiovascular protective effect of oestrogen replacement therapy in peri- and postmenopausal women. One study demonstrated a significant reduction in low density lipoprotein and a significant increase on high density lipoprotein in perimenopausal women treated with a 5 or 10 µg releasing T-LNG IUS (Wollter-Svensson *et al.*, 1995). The low doses of LNG did not reverse the beneficial effects on lipid metabolism usually seen after oestradiol administration.

Intrauterine progestogen delivery for endometrial suppression in the perimenopause is highly practical, as it combines the benefits of prevention of endometrial proliferation and treatment of menorrhagia and hyperplasia, if present. In addition, the potent contraceptive effect of locally administered LNG is highly desirable, as many perimenopausal women run considerable risk of unintended pregnancy (Grimes, 2001). Intrauterine drug delivery may therefore constitute a welcome reversible alternative to other contraceptive options that may be less suitable at this age.

Treatment of menorrhagia

Menorrhagia, defined as regular but heavy menstrual bleeding of >80 ml is a common disorder (Janssen *et al.*, 1997). The prevalence is between 9 and 28% of women aged 16–45 years and increases with age (Edlund *et al.*, 1994). Approximately 30% of referrals for gynaecological treatment are for menorrhagia, often leading to surgical intervention if conservative treatment (e.g. contraceptive pills, progestogens, fibrinolytic inhibitors and prostaglandin inhibitors) fails. In the USA, 700,000 hysterectomies are performed each year, of which 30% are for excessive menstrual bleeding. In the UK 40% of the 100,000 hysterectomies are performed for that reason. Idiopathic menorrhagia is the most common form of menorrhagia when no underlying cause (e.g. uterine and endometrial abnormalities, systemic coagulation defects) can be found. 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 (Cameron and Smith, 1992).

When menstrual blood loss exceeds 80 ml, the incidence of anaemia (haemoglobin <12 g/dl) is increased significantly (Janssen *et al.*, 1995). Anaemia is one of the most widespread, and most neglected, nutritional deficiency diseases in the world today (WHO, 1993). Iron deficiency with depletion of iron stores and/or anaemia predisposes the women to ill health and disease. In addition, women with menorrhagia are often

prevented from leading normal lives, their condition causing severe social embarrassment and repudiation by their partner.

Recently, new less invasive treatment options have been developed. Endometrial ablation techniques and classical endometrial resection have their value but are still very costly, although significantly cheaper than hysterectomy. They are also irreversible. The IUS releasing 20 µg T-LNG (Mirena®) has shown a dramatic decrease in menstrual blood loss in nearly all women and amenorrhoea in 20% or more due to profound endometrial atrophy (Luukkainen, 1986; Andersson *et al.*, 1994). Lähteenmäki *et al.* demonstrated that the T-LNG IUS (Mirena®) can replace hysterectomy due to menorrhagia (Lähteenmäki *et al.*, 1998). Two-thirds of women involved in his study cancelled their decision to undergo hysterectomy because the treatment was successful. The median number of days of bleeding decreased from 7 in the 1st 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.

Clinical observations

To evaluate the effect on menstrual blood loss using the FibroPlant-LNG IUS, releasing 14 µg of LNG/day, 32 insertions were performed in fertile women between 31 and 51 years of age for the treatment of menorrhagia (Wildemeersch and Schacht, 2001a). Fifteen women were fitted with the FibroPlant-LNG IUS immediately following removal of a copper-bearing IUD, who developed excessive bleeding. To discriminate between menorrhagia and normal menstrual blood loss, women were evaluated using a simple visual assessment technique. The trial covers a period from a minimum of 1 month up to 23 months. At the time of study analysis, 14 women had the FibroPlant-LNG IUS in place for periods in excess of 1 year and 29 women for 6 months.

All women reported greatly reduced bleeding. However, no cases of amenorrhoea resulting from endometrial suppression were encountered. The reduction of bleeding was significant after 1 month of treatment and decreased further over the next months to remain stable afterwards. The mean bleeding score before treatment was 338 (185–740) in the group with no prior IUD use and 368 (185–890) in the group with prior IUD use respectively, and dropped to a mean score of 70 (range 5–210) in the ‘no prior IUD use’ group and to a mean score of 52 (3–150) in the ‘prior IUD use’ group respectively after 1–23 months follow-up, which is highly statistically significant ($P < 0.001$). There was no statistical difference in bleeding scores before and during treatment between the two groups of women with or without prior copper IUD use.

The results of the study are in agreement with those obtained with the Mirena®LNG IUS (Andersson *et al.*, 1994; Sturridge and Guillebaud, 1996). The reduction of menstrual blood loss is at least 80% after insertion of the FibroPlant-LNG IUS in women with a normal uterus, which is highly significant. This occurs as early as 1 month after the start of the treatment due to strong endometrial suppression (Figure 5).

Intrauterine LNG delivery is probably the most effective, non-surgical and reversible treatment method of menorrhagia today and the best contraceptive choice in women with anaemia.

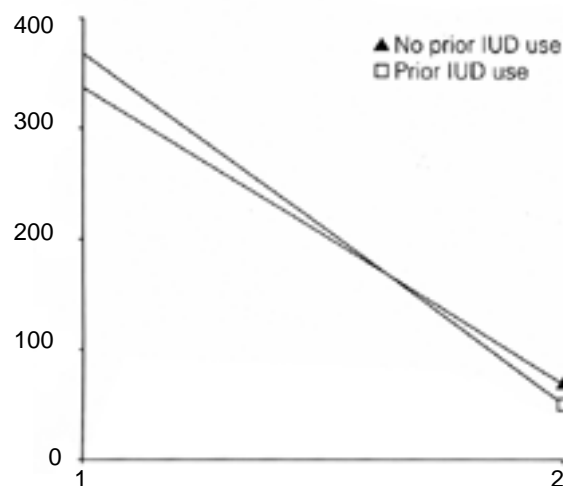


Figure 5. Illustration of the strong decrease of the menstrual blood loss scores from ‘before’ (1) to ‘during’ (2) treatment ($P < 0.001$) in two groups of women with no prior IUD use and with prior IUD use.

Women are highly satisfied with the results, even if irregular bleeding/spotting may occur during the first few months following insertion of the IUS. Counselling of women is therefore extremely important to reduce the number of unnecessary removals.

Contraception

When women are interviewed about their contraceptive preferences, it appears that the single most important property of a contraceptive is its effectiveness. Women would also greatly appreciate a contraceptive method that protects against sexually transmitted diseases in addition to its contraceptive effect. Long duration of action is also highly valued by women. For women who do not want to be pregnant again, the longer the method works, the better and most women would select a method that is reversible if they could choose. A ‘secret’ method (from husbands and other family members) is important for women in certain developing countries but not in the USA, although young women, especially adolescents, might wish to use contraceptives secretly. Women generally dislike methods that cause disturbance of the menstrual pattern. Amenorrhoea is strongly linked with the perception of ill-health, and women worry about the occurrence of a pregnancy (WHO, 1997).

Intrauterine contraception has many of the characteristics of an ideal contraceptive. The method is effective, safe, long-acting, reversible and discrete (WHO, 1987). It is the most cost-effective reversible method of contraception today. Worldwide use of IUD is widespread, but characterized by distinct regional variations (Grimes, 1998). Married women of reproductive age (WRA) in China and South East Asia account for three-quarters of all worldwide IUD usage. Within South East Asia, the highest incidence of IUD usage is found in Vietnam with 62% of WRA, whilst 40% of WRA in China use IUD. This percentage falls to 19% in Indonesia. In some European countries, the incidence of IUD usage is close to 20%. For example, in Scandinavia the figure is 18% of WRA

and in France 16%. IUD use in Latin America averages 6.2%, but in some countries such as Ecuador, Peru and Mexico, >20% of WRA use IUD.

In the USA, the use of IUD is currently very low. This is due to the adverse publicity caused by the Dalkon Shield, a plastic shield-shaped IUD commercially introduced in the USA in the early 1970s, which was associated with pelvic inflammatory disease (PID). Prior to the problems that arose with the Dalkon Shield, the IUD method of contraception was favoured by both US women and their physicians. 'In depth' research has since shown that the problems encountered with the Dalkon Shield were caused by the material used in one of its components (Tatum and Connell, 1989). Although PID is very seldom encountered with the new generation IUD, many women, especially in the USA, are reluctant to use this excellent method of contraception.

The challenge with intrauterine contraception is to apply new concepts to IUD design and activity to increase the attractiveness of the method to women and their physicians. New, improved, intrauterine technologies may revive the method and increase their prevalence of use (d'Arcanges, 2001). IUD suitable for emergency and post-abortual contraception are also welcome, to prevent unintended pregnancies and repeat abortions (Batár *et al.*, 1998).

Intrauterine contraceptive methods are particularly needed for young women, to reduce the rapidly increasing number of accidental pregnancies (Wildemeersch, 2001). In the past, the IUD was not recommended for use in young nulliparous women and those women with small uterine cavities. Traditionally, countries like France have been opposed to intrauterine contraception in nulliparous women. However, new concepts and innovation in IUD design have enabled a drastic reduction in the size and volume of new generation IUD, making them more acceptable for this group of women because they are small, effective and well tolerated and reduce the risk of expulsion. Unlike the pill, they are genuinely 'fit-and-forget'. In use, they are much more effective than pills in this age group (Trussell, 1998). Moreover they are long-acting and reversible. However, copper intrauterine devices do not offer protection against sexually transmitted infections (STI) and, therefore, they are not always the methods of first choice for teenagers. Such a protective effect has been observed with hormone-releasing intrauterine devices in women aged 25 years, although this finding was not confirmed in other studies (Andersson *et al.*, 1994). Nevertheless, in the current situation, they should be offered more frequently as first or second line methods, in combination with condoms if required, particularly after the first unintended pregnancy has occurred.

The WHO supports the use of suitable IUD in nulliparous women and suggests that the benefits of IUD generally outweigh the risks in women of any age, whether parous or not. In addition, the WHO approves the use of IUD in women <20 years, provided that these women are at low risk of STI and no PID occurred in the past 3 months (WHO, 1996). A review article was recently published on this topic. It was concluded that the risk of PID attributable to an intrauterine device is very low (Grimes, 2001). Calculation of this risk showed that the estimated risk is 0.15% even with a high STI

prevalence (Shelton, 2001). This low estimated risk argues for making IUD more available.

Clinical observations

The delivery of progestogens (i.e. LNG) in the uterine cavity for contraception is a new and a promising approach. With the currently available T-LNG IUS, the occurrence of amenorrhoea is 20%. Although this could be viewed as an advantage, amenorrhoea is problematic in many women, particularly the younger ones. Reducing the dose of LNG would result in a reduction of the amenorrhoea rate and make the method more acceptable to women. Besides, the occurrence of hormonal side-effects and perhaps irregular bleeding/spotting would also be lower. The hope to develop a smaller and low dose LNG-releasing IUS was expressed by one of the most important clinical experts involved with the clinical development of the T-LNG IUS (Andersson, 1998). Many women in both developed and developing countries could benefit from the positive effect on health resulting from a reduction in menstrual bleeding, in addition to the contraceptive effect. This is particularly important in regions where anaemia is endemic.

The large bulk of data with intrauterine LNG-delivery are derived from studies conducted with the T-LNG IUS (Luukkainen *et al.*, 1986; Sivin *et al.*, 1990). The results show that the system is a highly effective contraceptive method that also offers effective protection against ectopic pregnancy.

A major advantage of intrauterine devices and intrauterine systems over long-acting systemic hormonal methods is that they act locally, minimizing systemic effects. They have less impact on menstrual pattern after the first few months and, when low dose LNG intrauterine systems are used, they are less likely to cause initial spotting, amenorrhoea and hormonal side-effects.

Two preliminary studies with the FibroPlant-LNG IUS were conducted to evaluate the contraceptive performance, acceptability, side-effects and adverse events of the FibroPlant-LNG IUS, releasing 14 µg of LNG/day. An ancillary objective was to evaluate the effect of the new IUS on menstrual blood loss. In the first study, 54 insertions were performed in fertile women between 16 and 51 years of age for contraception (Wildemeersch and Schacht, 2000a,b). 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. Twenty-one women received the FibroPlant-LNG IUS in place for periods in excess of 1 year, during which no pregnancies occurred. All women reported greatly reduced bleeding.

In the second study, 109 insertions were performed in fertile women between 38 and 54 years of age for contraception. From these, 14 women were fitted with the FibroPlant-LNG IUS for the treatment of excessive bleeding as well as for contraceptive purposes. Eleven of these women had medium to large size uterine fibroids in addition to heavy menstrual flow. Four women had uterine fibroids without heavy

bleeding. The majority of women were followed-up for >1 year (range 1–38 months). No pregnancies occurred with the FibroPlant-LNG IUS (unpublished data).

Treatment of endometrial hyperplasia

Hyperplasia is characterized by a proliferation of the endometrial glands. In simple hyperplasia, the glands are normal but, in atypical hyperplasia, glandular abnormality is demonstrated both at cellular level and structurally. Simple hyperplasia rarely progresses to more severe conditions. Atypical adenomatous hyperplasia, on the other hand, has been observed to progress to adenocarcinoma of the uterus in 29% of the cases (Kurman *et al.*, 1985). In recent years, hyperplasia is caused most often by use of unopposed oestrogen for oestrogen replacement therapy (ERT) and tamoxifen for the treatment of breast cancer. Unopposed oestrogen has been found to increase the risk of adenocarcinoma of the endometrium significantly (Herrington and Weiss, 1993). The relative risk of developing endometrial cancer during tamoxifen treatment is 1.3–7.5 and is in the range of that of unopposed ERT (1.6–8.0) and causes a 2–3 fold increase in endometrial cancer (Assakis and Jordan, 1995). The abnormal vaginal bleeding which is seen in women with hyperplasia may vary from a few spots of blood to continuous bleeding for days and sometimes heavy bleeding. It is an alarm signal that should prompt thorough investigation. Endometrial sampling is an effective and reliable method of diagnosing endometrial cancer although a more systematic evaluation may be preferable in cases of adenomatous hyperplasia with or without atypia. Transvaginal ultrasound examination has been increasingly preferred as a method of evaluation to endometrial sampling because of its non-invasiveness and patient acceptability. When performed correctly, the negative predictive value of endometrial cancer is 100% when the antero-posterior endometrial thickness is 4 or 5 mm (Fleischer *et al.*, 1986; Gull *et al.*, 2000). It has become the first line examination using endometrial biopsy only when ultrasound is abnormal or if the uterine bleeding persists or recurs.

Simple hyperplasia is usually treated by oral administration of progestogens in sufficient dose and duration. However, if the treatment is discontinued, recurrence may occur. A response rate of ~70% is generally reported, with a persistence or recurrence rate of ~20% (Eichner and Abellera, 1971; Wentz, 1974). Local intrauterine treatment, which is much more potent, may therefore be preferable to oral treatment. Local delivery of levonorgestrel causes a uniform suppression of the endometrium and the changes are seen throughout the whole thickness of the mucosa. An implantable method also provides better patient compliance. The preferred treatment for adenomatous hyperplasia with atypia or adenocarcinoma of the endometrium is hysterectomy. However, successful treatment of early endometrial carcinoma has been reported with progestational therapy (Ferency and Gelfland, 1989). No reports have been found in the literature on local treatment with progestogens of early endometrial carcinoma.

In women using tamoxifen treatment for breast cancer, it has been recommended by several authors to insert a LNG-releasing IUS to avoid regular sampling and prevent endometrial proliferation (Van Liedekerke *et al.*, 1998;

Gardner *et al.*, 2000).

In women using oestrogen replacement therapy, endometrial hyperplasia can be prevented by the addition of progestogen to the oestrogen regimen. Several regimens have been designed (Archer, 1998). When cyclic progestogens are administered, reinitiation of uterine bleeding occurs in ~85% of women. Continuous-combined regimens, however, have been highly effective to reduce the occurrence of reinitiation of uterine bleeding but the regimen has been reported to have a high incidence of irregular uterine bleeding during the first 4–6 months of treatment. Systemic progestogens have an essentially anti-oestrogenic effect and can potentially counteract the beneficial effects of co-administered oestrogens. Furthermore, they may precipitate a number of hormonal side-effects such as mood changes, headache, sleepiness, mastalgia, nausea, hirsutism. They also induce vasoconstriction of oestrogenized vessels although some studies have been reassuring in this respect. The main concern, however, about progestogens compromising the potential cardioprotective actions of oestrogens rests in the recognition that oestrogen effects on the arterial physiology are important in preventing ischemic events and that progestogens could have an adverse effect on these actions (Furchgott and Zawadzki, 1980; Hulley *et al.*, 1998). Consequently, it has been proposed that the best method for delivering a progestogen to postmenopausal or climacteric women would seem to deliver it directly to the target structure, the endometrium, to avoid systemic effects (Henderson *et al.*, 1988; Sarrel *et al.*, 1995).

Clinical observations

Two previous studies using the T-LNG IUS in a small number of women with simple and atypical endometrial hyperplasia demonstrated a curative effect of the IUS (Perino *et al.*, 1987; Scarcelli *et al.*, 1988).

The effectiveness of the FibroPlant-LNG system was evaluated clinically and by ultrasound in 12 women with abnormal uterine bleeding in whom endometrial hyperplasia was diagnosed. Eight women complained of vaginal bleeding as a result of unopposed oestrogen stimulation. One woman consulted because of abnormal bleeding during tamoxifen treatment for breast cancer. Three other women had abnormal premenopausal bleeding. The histopathological diagnosis was 'simple hyperplasia' in seven women and 'atypical hyperplasia' in five women (adenomatous hyperplasia with atypia in three of them). In two women, endometrial polyp formation was found. In one woman, an invasive well-differentiated adenocarcinoma of the endometrium was found on endometrial biopsy obtained by conventional dilatation and curettage but this was not confirmed by two subsequent endometrial pipelle samplings.

Following treatment initiation, women were followed up for 6 months up to 3 years. After an initial short period of spotting, menstrual bleeding stopped completely in all women studied and endometrial atrophy developed. Slight, scanty and infrequent bloody discharge requiring no protection, or a small panty liner, occurred in most women during the first 3 months of treatment. All women developed a thin endometrium (<5

mm in thickness), as assessed by transvaginal ultrasound, and are continuing in the study.

These results suggest that the FibroPlant-LNG system is an effective method for suppressing the endometrium in women with hyperplasia resulting in atrophy of the endometrium and amenorrhoea (unpublished data).

Treatment of dysmenorrhoea

Dysmenorrhoea is described as a very common gynaecological problem. In articles about the subject, it is mentioned that dysmenorrhoea is typical in young, nulliparous women. About 50% of them suffer from pain during menstruation and some 10–20% are absent from work for 1 or 2 days each or every second menstruation (Begsjö *et al.*, 1975; Andersch and Milsom, 1982). Studies have also shown that dysmenorrhoea improves or disappears after the first birth, but also that menstrual pain is not uncommon in older women. As high as 30% of 30- to 40-year-old women still complain of menstrual pain.

Primary or spasmodic dysmenorrhoea should be distinguished from secondary dysmenorrhoea. In primary dysmenorrhoea, 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 dysmenorrhoea 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 dysmenorrhoea: non-steroidal anti-inflammatory drugs (NSAID), 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 dysmenorrhoea. For secondary dysmenorrhoea, surgery (e.g. hysterectomy, endometrial ablation) can be helpful if medical treatment fails (Lumsden, 1998).

Clinical observations

It is not surprising that the LNG-releasing T-shaped IUS has been used successfully in primary and secondary dysmenorrhoea, 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 (Sivin and Stern, 1994). The rationale is that the localized activity of LNG is many times stronger than the effect obtained following oral treatment. This enhanced activity could be useful for the intrauterine treatment of dysmenorrhoea associated with excessive menstrual bleeding.

The LNG IUS was also effective in alleviating dysmenorrhoea in the presence of rectovaginal endometriosis, which is commonly associated with severe dysmenorrhoea, dyspareunia, and pelvic pain (Fedele *et al.*, 2001).

The FibroPlant-LNG IUS was evaluated in 18 women with primary and secondary dysmenorrhoea (Wildemeersch *et al.*, 2001). Eighteen insertions were performed in women between 16 and 52 years of age. Four insertions were done in nulligravid women. Eight women were categorized as having primary dysmenorrhoea and 10 as having secondary dysmenorrhoea. Twelve women complained of heavy bleeding. Three women had significant fibroids and three were suspected of having adenomyosis.

At the time of study analysis, 12 recruited women had at least 12 months follow-up, with six between 3 months and 1 year. All women reported much reduced pain, or no pain at all, and strongly reduced bleeding which started 1 month after insertion of the FibroPlant-LNG IUS. There was one exception, a woman who had significant fibroids. She reported significantly reduced bleeding, but this was not as pronounced as in the other women in the study. All women are continuing to use the method.

The study results suggest that the FibroPlant-LNG IUS is highly effective in primary as well as secondary dysmenorrhoea. The treatment also markedly decreases menstrual pain in conjunction with heavy menstrual bleeding, including in women with significant fibroids and heavy bleeding. Furthermore, the frameless design of the FibroPlant-LNG IUS avoids incompatibility problems. This is a significant advantage, especially in women with dysmenorrhoea, who may also have a distorted uterine cavity as may be the case in the presence of fibroids.

Treatment of uterine fibroids

Uterine myoma (leiomyoma, fibroid) is a very common disease. Leiomyomata occur with an incidence of up to 77% (Cramer and Patel, 1990). They are often asymptomatic but some 25–50% of women will experience symptoms such as menorrhagia and pelvic discomfort. About 5% of fibroids are intracavitary and submucosal and are most difficult to treat (Buttram and Reiter, 1981; Donnez *et al.*, 1996). Hysterectomy is still the most commonly used procedure, although medical treatments are preferable (Vollenhoven *et al.*, 1990; Cramer *et al.*, 1995). Uterine fibroids are responsible for 30% of hysterectomies. Recently, new conservative treatment options have been developed such as treatment with gonadotrophin-releasing hormone (GnRH) analogues and LNG IUS (Donnez *et al.*, 1999; Nisolle and Donnez, 1999). Lähteenmäki *et al.* demonstrated that the LNG IUS Mirena® can replace hysterectomy due to menorrhagia but this study was not conducted in women with uterine fibroids (Lähteenmäki *et al.*, 1998).

Uterine fibroids are often accompanied by excessive menstrual bleeding, as both conditions increase significantly with age. As they are extremely common, it is logical that researchers look for medical treatments that are appropriate for the management of uterine fibroids, particularly if associated with menorrhagia. Several conservative medical treatments have been tested.

The role of GnRH agonists in the treatment of uterine leiomyomata is limited, as most leiomyomata return to their initial size within 4 months of cessation of the therapy (Nisolle and Donnez, 1999). GnRH agonists are mainly useful when used preoperatively to reduce the myoma size.

Treatment of leiomyomata with progestogens and anti-oestrogens is based on the suggestion that leiomyomata are ovarian steroid dependent. The results of progesterone treatment have been poor, however, and no studies have ever demonstrated the benefit of progesterone alone (Donnez *et al.*, 1999).

Tamoxifen inhibits breast cancer cells by its high affinity for the oestrogen receptor. However, on the endometrial level, tamoxifen may induce endometrial changes and endometrial cancer. While acting as an anti-oestrogen on the breast, tamoxifen has an opposite effect on the endometrium as it acts as a partial oestrogen agonist, rather than as an antagonist (Assakis and Jordan, 1995).

A new compound, ICI 182,780, a 'pure' anti-oestrogen, has been clinically tested. It was found to inhibit endometrial growth and cause shrinkage of uterine fibroids. The disadvantages found were systemic symptoms such as headache and mild bone resorption.

Clinical observations

It has been shown that the T-LNG IUS is a very useful, effective, non-surgical and reversible treatment method of menorrhagia in women with fibroids (Sivin and Stern, 1994). Singer and Ikomi reported a reduction in fibroid volumes after 6–18 months of use (Singer and Ikomi, 1994). In contrast, however, Maruo *et al.*, using the T-LNG IUS in women with uterine fibroids and menorrhagia, did not find an effect on myoma volume as measured by magnetic resonance imaging (MRI) but the effect on reducing the amount of menstrual blood was significant with the exception of submucosal fibroids (Maruo *et al.*, 1998).

To evaluate the effect on menstrual blood loss in women with uterine myomas, FibroPlant-LNG IUS was tested in 14 women with significant uterine fibroids complaining of heavy menstrual bleeding (Figure 6) (Wildemeersch and Schacht, 2001b). Fourteen insertions were performed in premenopausal women between 39 and 48 years of age for the treatment of menorrhagia. The effect on menstrual blood loss was evaluated using a visual assessment technique. Women were followed-up for at least 12 months (range 12–30 months).

At the time of study analysis, the total number of women-months was 283. All women except one reported greatly reduced bleeding. Treatment was unsuccessful in two women due to abnormalities present in the uterine cavity. The presence of intracavitary pathology (e.g. submucous fibroids, polyps) should be suspected if reduction of bleeding cannot be obtained. Treatment failure in the presence of submucosal fibroids is caused by blood vessels which proliferate in the endometrium overlying the fibroid which can cause 'heavy' bleeding. These vessels are not present in subserosal fibroids (Smith, 1999).

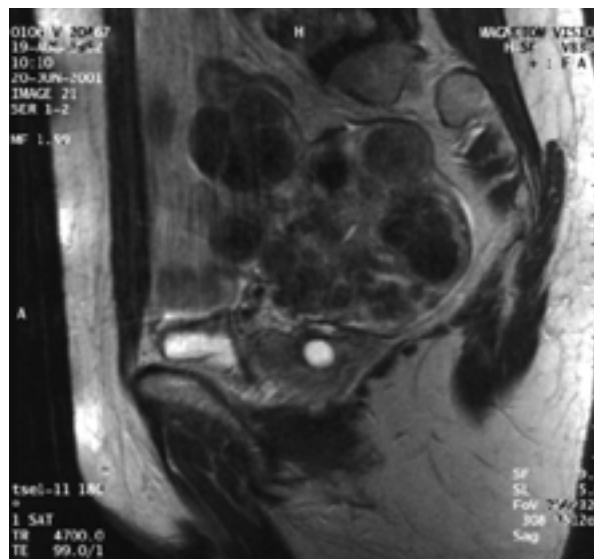


Figure 6. MRI in patient with multiple uterine fibroids responding very well to intrauterine treatment with LNG, with the FibroPlant-LNG IUS in the middle of the picture.

The mean bleeding score before treatment was 465 (185–960) and dropped to a mean score of 100 (range 5–300) after a minimum of 12 months of treatment which is highly statistically significant ($P < 0.001$). In eight women, the bleeding reduced to very low scores. An effect on the size of the uterine fibroids could not be demonstrated.

This study does not suggest that LNG-release in the uterine cavity is capable of reducing the size of the myomata in women at reproductive age. Decrease in size of leiomyomata is usually seen in menopausal women. It is doubtful if intrauterine delivery of LNG can result in a reduction in the size of the myomata.

Conclusions

User non-compliance is an ubiquitous phenomenon occurring particularly in young women but also in women using conventional menopausal treatment regimens. Scientists as well as marketers are puzzled. How can we improve this situation? The reward could be substantial if women would take contraceptive pills correctly and consistently. This is not likely to occur. One can be certain that much fewer unintended pregnancies and induced abortions would occur if long-term methods would be used more often (Polaneczky *et al.*, 1994; Templeman *et al.*, 2000). In peri- and postmenopausal women this would lead to a maximization of the long-term benefits of HRT.

One of the ways forward seems to us to design and develop drug delivery systems which act locally on the target cells offering enhanced effectiveness and reduced systemic side-effects. Intrauterine drug delivery is highly appropriate to obtain this objective. The development of support-free drug delivery carriers has the additional advantage of coping with support-specific problems. Moreover, the space gained can be used to maximize the drug delivery capacity of the uterine

system to create IUS that last longer, e.g. 10–20 years. Imagine, a single, few minutes office procedure providing effective, reversible and discrete contraception lasting for years without the concern about health and non-compliance related issues. Morbidity and mortality are undeniably linked with more invasive methods and systemic hormonal contraceptives. Unquestionably, there would be a number of additional important advantages such as helping the immense problem of anaemia in certain regions of the world by reducing the amount of bleeding.

With regard to cost, the expense and effort to develop a new method is very high indeed. The cost to the user in the rich countries is usually a factor of minor importance. However, the accessibility of a method in the public sector of less developed countries is largely dependent on the price governments and donors are willing to pay for it. Widespread use minimizes costs thus reducing price.

Simplicity in applying a method is also one of the major determinants in the prevalence of use especially when dealing with intrauterine methods. Improving the insertion technique to reduce the learning curve has received constant attention from the developers of the FibroPlant intrauterine system.

Summarizing, the low-dose FibroPlant-LNG intrauterine system, releasing 14 µg/day, combines several important benefits for women's health as follows.

Hormone replacement therapy: The system provides effective endometrial suppression in perimenopausal and postmenopausal women using ERT. Of considerable advantage in many perimenopausal women is the additional contraceptive effect of the system and its effect on reducing menstrual bleeding. The reduced dose of the FibroPlant-LNG IUS results in a virtual absence of hormonal side-effects. Clinical results confirm the high patient satisfaction and continuance of the method; a prerequisite to maximize the long-term health benefits of HRT.

Treatment of menorrhagia: FibroPlant-LNG IUS is effective in significantly reducing the amount of menstrual blood loss in women with menorrhagia. The therapeutic effect of this contraceptive method is highly desirable, particularly in women with heavy bleeding or anaemia in developing countries, as other treatment modalities are less effective, more costly, more invasive or inaccessible.

Contraception: The preliminary studies with the low-dose FibroPlant-LNG IUS used for contraception confirm those conducted with the T-LNG IUS (Mirena®). The rates of amenorrhoea and hormonal side-effects are low and can be attributed to the low release rate of the IUS. Spotting in the beginning may also be reduced, but further studies should be conducted in this respect. Discomfort during use of the FibroPlant IUS is avoided because of the frameless and flexible design of the IUS.

Endometrial hyperplasia: FibroPlant-LNG IUS is effective for the treatment of simple and probably atypical hyperplasia as well. FibroPlant-LNG IUS could be useful in the prevention of endometrial changes in women using tamoxifen for the

preventive or adjuvant treatment of breast cancer.

Dysmenorrhoea: FibroPlant-LNG IUS is an effective method for the treatment of primary and secondary dysmenorrhoea. The absence of a frame is particularly advantageous in these women. The narrow insertion tube (3.8 mm) allows easy passage through the cervix.

Fibromyoma: FibroPlant-LNG IUS is an effective method to treat menorrhagia in women with intramural and subserosal fibroids. The simple physical design characteristics of the system avoid incompatibility problems. FibroPlant-LNG IUS does not appear to reduce the size of the fibroids. FibroPlant-LNG IUS may be a highly attractive cost-effective treatment option to many women and avoid the high cost of surgery and other more invasive treatment procedures.

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