ELSEVIER

European Journal of Obstetrics & Gynecology and Reproductive Biology 4153 (2001) 1–6

EUROPEAN JOURNAL OF OBSTETRICS & GYNECOLOGY AND REPRODUCTIVE BIOLOGY

www.elsevier.com/locate/ejogrb

The effect on menstrual blood loss in women with uterine fibroids of a novel "frameless" intrauterine levonorgestrel-releasing drug delivery system: a pilot study

D. Wildemeersch[a,*], E. Schacht[b]

[a]Central Research, Technology Park Zwijnaarde, Piers de Raveschootlaan 125, 8300 Knokke, Ghent, Belgium
[b]Polymer Research Group, Department of Chemistry, University of Ghent, Ghent, Belgium

Received 18 May 2001; received in revised form 20 August 2001; accepted 28 August 2001

Abstract

Objective: To evaluate the effect on menstrual blood loss, in women with uterine fibroids, of a novel "frameless" intrauterine drug delivery system (IUS), FibroPlant-levonorgestrel (LNG), releasing 14 μg of LNG per day. *Study Design*: An open label, non-comparative ongoing pilot study. 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 simple visual assessment technique. Women were followed-up for at least 12 months (range 12–30 months). *Results*: At the time of study analysis the total number of women-months was 283. All women, except one reported greatly reduced bleeding. In two women, the treatment failed although both reported reduced bleeding. One failure (patient no. 4) was due to the presence of a large endometrial polyp. This patient underwent hysterectomy. The other women (patient no. 1) had submucosal fibroids. She refused hysterectomy and is continuing treatment. In the other 12 patients, reduction of bleeding was appreciable after one month of treatment and tended to decrease further over the next months to stabilize afterwards. 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. Significant spotting was rare after the first 3 months following insertion. Neither complications (e.g. infection, expulsion or perforation) nor pregnancies occurred. The FibroPlant-LNG IUS was well tolerated by all women involved in the study and no systemic hormonal side effects were reported. *Conclusion*: This study suggests that FibroPlant-LNG IUS is effective to significantly reduce the amount of menstrual blood loss in women with menorrhagia in the presence of intramural and subserosal fibroids and can avoid surgery. The strong endometrial suppression is the principal mechanism explaining the effect on menstrual blood loss of the IUS. The two failures probably explain that a successful treatment in women with endometrial abnormalities (e.g. polyps, submucous fibroids) is unlikely with the IUS. The low daily release rate of LNG from the FibroPlant-LNG IUS results in a low incidence of hormonal side effects. The simple design characteristics and revolutionary anchoring system account for minimizing the occurrence of complaints of pain and expulsion. The flexible fibrous delivery system adapts to cavities of every size even when severely distorted. © 2001 Published by Elsevier Science Ireland Ltd.

Keywords: "Frameless" intrauterine system (IUS); Levonorgestrel (LNG); Uterine fibroids; Menorrhagia; Pilot study

1. Introduction

Uterine myoma (leiomyoma, fibroid) is a very common disease. Leiomyomas occur with an incidence of up to 77% [1]. They 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 [2,3]. Hysterectomy is still the most commonly used procedure although medical treatments are preferable [4,5]. Uterine fibroids are responsible for 30% of hysterectomies [1]. Recently, new conservative treatment options have been developed such as the treatment with GnRH analogs and the levonorgestrel-releasing intrauterine system (LNG IUS) [6,7]. Lähteenmäki et al. demonstrated that the LNG IUS Mirena® can replace hysterectomy due to menorrhagia [8]. This study, however, was not conducted in women with uterine fibroids.

This paper reports on the results of treatment of fibroid-associated menorrhagia using a new "frameless" LNG-releasing drug delivery system, the FibroPlant-LNG IUS.

* Corresponding author. Tel.: 32-50-600-900; fax: +32-50-622-429.
E-mail address: dirk.wildemeersch@contrel.be (D. Wildemeersch).

PII: S0301-2115(01)00555-3

The physical design of FibroPlant-LNG IUS has been optimized in order to provide optimal tolerance and avoid incompatibility problems. FibroPlant-LNG IUS releases a lower dosage of LNG (14 μg per day) than the Mirena® IUS (20 μg per day). Previous clinical studies conducted with the FibroPlant-LNG IUS have demonstrated its endometrial suppressive effects in menorrhagic women with normal uteri reducing the amount of bleeding significantly [9].

2. Materials and methods

2.1. Description of the FibroPlant-LNG IUS

The FibroPlant-LNG IUS consists of a fibrous delivery system of 3 cm long and 1.2 mm in diameter that releases 14 μg of LNG daily. The fibrous delivery system is fixed to an anchoring filament by means of a metal clip positioned 1 cm from the anchoring knot. The anchoring knot at the proximal end of the thread is implanted into the myometrium of the uterine fundus using an insertion instrument, thus permanently securing the implant in the uterine cavity (Fig. 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 (Fig. 2). Measuring the distance between the surface of the uterus and the metal clip (S–S distance) indicates whether the FibroPlant IUS has been properly anchored.

When compared with the Mirena® LNG IUS, the FibroPlant-LNG IUS has no frame, it is therefore completely flexible, with the ability to adapt to uterine cavities of every size and shape.

In vitro studies show that the rate of LNG release is constant over several years. The duration of release is at least 3 years. The fibrous delivery system was developed in collaboration with the Polymer Research Group, Department of Chemistry, University of Ghent, Belgium.

Fig. 1. The FibroPlant-LNG IUS after insertion in a uterine model.

2.2. Screening and selection

All women to be included in the study were screened for their clinical suitability for IUD insertion. The following were excluded: clinical cervicitis or vaginitis (infection should be ruled out); history of PID, genital actinomycosis or chronic pelvic pain; blood clotting disorder; known or suspected uterine or cervical malignancy; detectable 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.

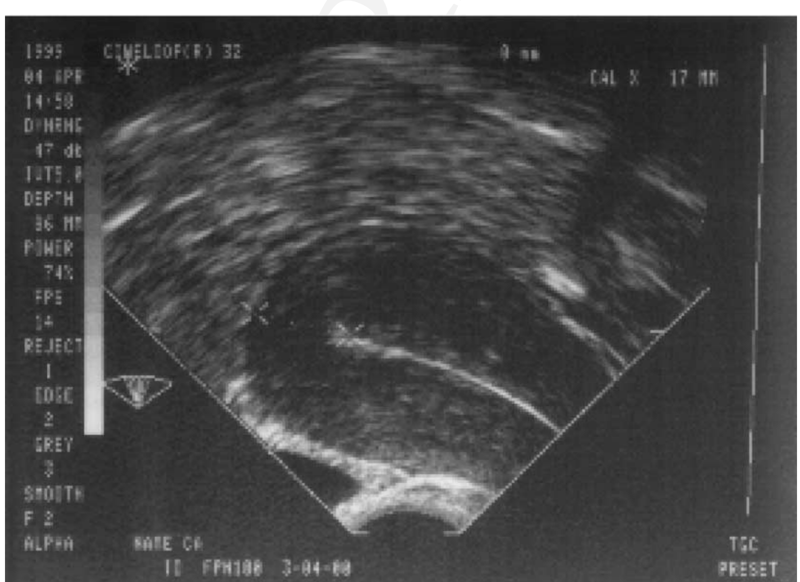

Fig. 2. Ultrasound picture of FibroPlant-LNG in situ.

Women with uterine fibroids and menorrhagia were selected to participate in the study. Transvaginal ultrasound (TVU), and in some cases magnetic resonance imaging (MRI), was performed to evaluate the uterine status. 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.

Type IV: single or multiple intramural and subserosal fibroids. Suspicion or evidence of submucosal fibroids.

To discriminate between menorrhagia and normal menstrual blood loss, a simple visual assessment technique was used as described by Janssen et al. [10]. Information on menstrual bleeding was obtained by interview prior to entering the study using a picturial chart form to describe the degree to which the sanitary wear was soiled. A score was calculated by multiplying the number of slightly, moderately and heavily soiled pads and tampons by 1, 5 and 20 for pads and 1, 5 and 10 for tampons, respectively, according to their degree of staining (Fig. 3). It should be noted that no standard type of sanitary material was used. If women used 'maxi' pads or 'super' tampons, which was often the case, the calculation was not adapted and was done as they were using regular sanitary wear. Women with menorrhagia wish to use 'maxi' pads or 'super' tampons, or even 'double' protection, during their 'heaviest' days or during the night, and then switch to normal pads and tampons when the amount of bleeding decreases. A score of 185 was used as cutoff point as this score has a predictive value of 85% to be consistent with menorrhagia.

Fig. 3. MRI in patient no. 13 with large size uterine fibroids responding very well to intrauterine treatment with LNG.

2.3. Admission and insertion of the IUS

One investigator (DW) performed all insertions. Written informed consent was obtained and the Ethics Committee of the Ghent University, Belgium, approved the study. Patients were 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 infections (STIs). Following insertion, vaginal ultrasound was performed to locate the device in the uterus as described previously.

Table 1
Characteristics of the study group; visual bleeding scores before and during treatment; and type of fibroid(s)[a]

Initials	Age at insertion	GP	Insertion date and score	Last follow-up date and score	Staging/comment
PC	43	G1P1	20 October 1998 (500)	12 April 2001 (300)	Probably type IV dysmenorrhea submucosal fibroids
VDCD	43	G2P2	12 March 1999 (750)	5 May 2001 (195)	Type IV dysmenorrhea submucosal fibroids
DTM	48	G1P1	15 March 1999 (372)	3 May 2001 (66)	Type IA denomyosis
BB	44	G0P0	18 March 1999 (250)	19 December 2000 (150)	Type IV hysterectomy (large endometrial polyp)
SL	46	G2P2	30 April 1999 (420)	8 January 2001 (110)	Type III
TM	44	G3P3	14 May 1999 (185)	18 December 2000 (35)	Type I
BM	42	G2P2	2 July 1999 (375)	7 May 2001 (60)	Type III
SM	39	G2P2	24 August 1999 (190)	3 May 2001 (5)	Type I
MH	47	G1P1	1 October 1999 (960)	4 May 2001 (25)	Type I dysmenorrhea
VM	49	G1P1	30 October 1999 (400)	2 March 2001 (150)	Type II–III
DG	46	G1P1	4 November 1999 (400)	6 February 2001 (180)	Type III
VDVN	39	G1P1	16 November 1999 (450)	2 May 2001 (40)	Type III
DA	47	G1P1	6 December 1999 (515)	3 April 2001 (75)	Type IV
TD	47	G1P1	25 January 2000 (600)	22 January 2001 (8)	Type III dysmenorrhea

[a] Clinical and ultrasonographic staging: 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. Type IV: single or multiple intramural and subserosal fibroids. Suspicion or evidence of submucosal fibroids.

2.4. 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 women were interviewed about their bleeding patterns and any side effects or adverse reactions. On each occasion a full gynecological examination including a TVU was performed to exclude any abnormalities and to locate the implant.

To measure the effect of FibroPlant-LNG IUS on the amount of menstrual blood loss, the pictural chart form was completed. The purpose of this simple evaluation was to obtain clinical measurable information of the effect of the FibroPlant-LNG IUS on the amount of bleeding on an individual basis.

3. Results

At the time of study analysis 14 women fitted with Fibro-Plant-LNG, who complied with the study criteria, had the IUS in place for periods in excess of 1 year (range 12–30 months). The total number of women-months was 283. The events were evaluated on an individual basis (Table 1). Statistical analysis was carried out according to the method of statistical analysis of variance for repeated measurements, $P < 0.05$ denoting statistical significance [11].

All women reported greatly reduced bleeding, except one (patient no. 1). In two women, the treatment failed although both reported reduced bleeding. One failure (patient no. 4) was due to the presence of a large endometrial polyp. This

Table 2
Descriptive statistics: age and visual bleeding score (VBS) before and during treatment

	Age	VBS before treatment	VBS during treatment
Mean	45	455	100
S.D.	3	210	85
Median	45	410	71
Range	39–49	185–960	5–300

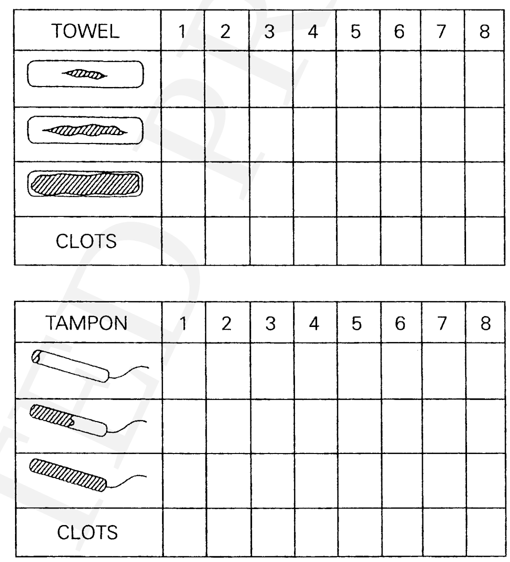

Fig. 4. The pictural chart form. The numbers 1–8 represent the consecutive days of a bleeding episode.

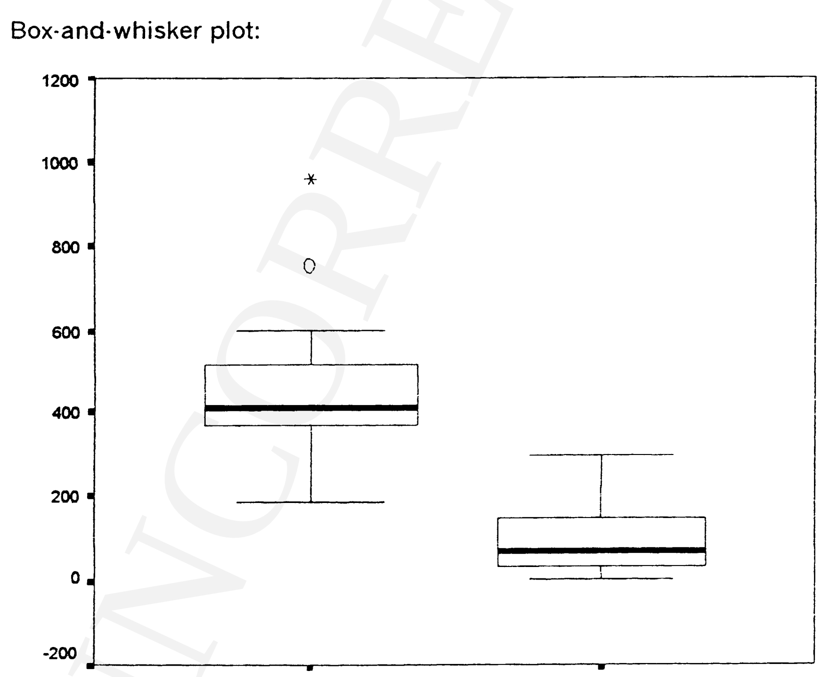

Fig. 5. Paired comparison of VBS before vs. during treatment. Wilcoxon matched-pairs signed-ranks test: $P = 0.001$. Paired Student's t-test: $P = 0.001$.

patient underwent hysterectomy. The other women (patient no. 1) had submucosal fibroids. She refused hysterectomy and is continuing treatment. In the other 12 patients, reduction of bleeding was appreciable after 1 month of treatment and tended to decrease further over the next months to stabilize afterwards. The mean bleeding score before treatment was 465 (185–960) and dropped to a mean score of 100 (range 5–300) after treatment which is highly statistically significant ($P < 0.001$). In eight women, the bleeding reduced to very low scores Table 2.

An effect on the size of the uterine fibroids could not be demonstrated. Fig. 3 shows a MRI, taken 17 months after treatment initiation, of a woman with large fibroids who responded very well to the local LNG treatment.

Neither complications (e.g. infection, expulsion or perforation) nor pregnancies occurred. The FibroPlant-LNG IUS was well tolerated by all women involved in the study and no systemic hormonal side effects were reported (Figs. 4 and 5).

All insertions were successful. Significant spotting was rare in the majority of women after the first 3 months following insertion. Neither complications (e.g. infection, expulsion or perforation) nor pregnancies occurred. The FibroPlant-LNG IUS was well tolerated by all women involved in the study and no systemic hormonal side effects were reported.

4. Discussion

Menorrhagia is defined as regular but heavy menstrual bleeding of more than 80 ml from a secretory endometrium. When menstrual blood loss exceeds 80 ml, the incidence of anemia (hemoglobin less than 12 g/dl) is increased significantly [12]. Iron deficiency with depletion of iron stores and/or anemia predisposes the women to ill health and disease. In addition, women with menorrhagia are often prevented from leading normal lives causing severe social embarrassment and repudiation by the partner.

Menorrhagia increases significantly with age. Although menorrhagia is frequent in young women, the percentage of women with menorrhagia is significantly higher above 40 years of age [13]. This is mainly explained by the higher frequency of uterine pathology, such as fibroids and polyps, which are more common during the premenopausal years.

As uterine fibroids are extremely common, it is logical that researchers look for medical treatments that are appropriate for the management of menorrhagia in women with uterine fibroids. Several conservative medical treatments have been tested.

The role of GnRH agonists in the treatment of uterine leiomyomas is limited as most leiomyomas return to their initial size within 4 months of cessation of the therapy [6]. GnRH agonist are mainly useful when used preoperatively to reduce the myoma size.

Treatment of leiomyomas with progestogens and antiestrogens is based on the suggestion that leiomyomas are ovarian steroid dependent. The result, however, of progesterone have been poor and no studies have ever demonstrated the benefit of progesterone alone [7].

Tamoxifen inhibits breast cancer cells by its great affinity for the estrogen receptor. However, on the endometrial level tamoxifen may induce endometrial hyperplasia and endometrial cancer. While acting as an antioestrogen on the breast, tamoxifen has an opposite effect on the endometrium as it act as a partial estrogen agonist, rather than as an antagonist [13].

A new compound, ICI 182,780, a 'pure' antiestrogen 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.

To avoid systemic systems, local therapy might optimize innovative approaches. Local therapy has been widely used for contraception but it has not been used to control leiomyoma symptoms. Intrauterine treatment might target myoma specific symptoms better and be more effective in reducing pelvic pressure due to the size of the tumor, and abnormal uterine bleeding.

The FibroPlant-LNG IUS, releasing 14 μg of LNG per day, was developed to provide a strictly localized effect and thus minimize systemic hormonal side effects. A recent study conducted in 32 women with menorrhagia demonstrated a reduction of menstrual blood loss of at least 80% after insertion of the FibroPlant-LNG IUS in women with a normal uterus. The reduction in bleeding occurred as early as 1 month after the start of the treatment due to strong endometrial suppression [9].

The present study confirms our previous results in women with menorrhagia with normal uteri. Twelve out of 14 women admitted in the study were successfully treated. The treatment, however, was unsuccessful in two women due to abnormalities present in the uterine cavity. It follows that, if reduction of bleeding cannot be obtained, the presence of intracavitary pathology (e.g. submucous fibroids, polyps) should be suspected. 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 [14].

This study does not suggest that LNG-release in the uterine cavity is capable of reducing the size of the myomas in women at reproductive age. Decrease in size of leiomyomas is usually seen in menopausal women. The present study was conducted in premenopausal women. Local delivery of other drugs such as mifepristone, with its strong antiprogestin activity and antiestrogenic effect at the endometrial level, may be more suitable to reduce the size of the fibroid tumors. No studies with intrauterine delivery of mifepristone have been conducted so far. Orally administered mifepristone has been highly satisfactory in this respect.

The LNG IUS is a very useful, effective, non-surgical and reversible treatment method of menorrhagia in women harboring fibroids. In women with a normal uterus, the success rate is close to 100%. In the presence of fibroids, however, the success rate is not consistent. This was also shown by other studies conducted in women with fibroids [15].

It is doubtful if intrauterine delivery of LNG can result in a reduction in the size of the myomas.

Irregular bleeding/spotting can occur in some women during the first months following insertion of the IUS and is the most common side effect. This side effect can be minimized by inserting the FibroPlant-LNG IUS during menstruation.

An additional advantage of the LNG IUS is the highly appeasing effect of the treatment in four women with dysmenorrhea in this study confirming a separate study conducted with the FibroPlant IUS in women with primary and secondary dysmenorrhea [16].

The low-dosage FibroPlant IUS has a low incidence of hormonal side effects such as acne, mood changes, headache, sleepiness, mastalgia, nausea, and hirsutism which are more likely when higher LNG doses are used [17].

The FibroPlant-LNG IUS, has a simple physical design avoiding incompatibility problems seen with both conventional IUDs and the Mirena® T-shaped LNG-IUS. Together with its beneficial effects on menstrual blood loss and its high contraceptive performance, FibroPlant-LNG IUS maybe a highly attractive cost-effective treatment option to many women and avoid the high cost of surgery and other more invasive treatment procedures.

Acknowledgements

The authors greatly acknowledge Prof. Dr. G. De Moor and G. Van Maele, Dr. Sc. of the Department of Medical Informatics and Statistics, University Hospital Gent, Belgium for providing statistical data analysis for the study.

References

[1] Cramer SF, Patel A. The frequency of uterine leiomyomas. Am J Clin Pathol 1990;94:435–8.

[2] Buttram VC, Reiter RC. Uterine leiomyomas: etiology, symptomatology and management. Fert Steril 1981;36:433–45.

[3] Donnez J, Schindler AE, Wall weiner D, Audebert A. Fibroids: management and treatment. In: Lunenfeld B, Insler V, editors. GnRH analogues: the state of the art 1996. Carnforth, UK: Parthenon Publishing, 1996. p. 71–82.

[4] Vollenhoven BL, Lawrance AS, Healy DL. Uterine fibroids: a clinical review. Br J Obstet Gynaecol 1990;97:285–98.

[5] Cramer SF, Hoiszny JA, Leppert P. Epidemiology of uterine leiomyomas. With an etiologic hypothesis. J Reprod Med 1995; 40:595–600.

[6] Nisolle M, Donnez J. Medical management of uterine fibroids: short-term therapy with GnRH agonists. In: Brosens I, Lunenfeld B, Donnez J, editors. Pathogenesis and medical management of uterine fibroids. Carnforth, UK: Parthenon Publishing, 1999. p. 113–19.

[7] Donnez J, Gillerot S, Squifflet J, Nisolle M. Progestogens and antiprogestogens. In: Brosens I, Lunenfeld B, Donnez J, editors. Pathogenesis and medical management of uterine fibroids. Carnforth, UK: Parthenon Publishing, 1999. p. 121–8.

[8] Lähteenmäki P, Haukkamaa M, Puolakka J, et al. Open randomized study of use of levonorgestrel-releasing intrauterine system as alternative to hysterectomy. Br Med J 1998;316:1122–226.

[9] Wildemeersch D, Schacht E. Treatment of menorrhagia with a novel frameless intrauterine levonorgestrel-releasing drug delivery system: a pilot study. Eur J Contraception Reprod Health Care 2001;6:93–101.

[10] Janssen CA, Scholten PC, Heintz APM. A simple visual assessment technique to discriminate between menorrhagia an normal menstrual blood loss. Obstet Gynecol 1995;85(6):977–82.

[11] Altman DG. Practical statistics for medical research. Chapman & Hall, London, 1995.

[12] Janssen CA, Scholten PC, Heintz APM. Menorrhagia: a search for epidemiological risk markers. Maturitas 1997;28:19–25.

[13] Assakis VJ, Jordan VC. Gynecological effects of tamoxifen and the association with breast carcinoma. Int J Gynecol Obstet 1995;49: 241–57.

[14] Smith S.K. Growth factors. In: Brosens I, Lunenfeld B, Donnez J, editors. Pathogenesis and medical management of uterine fibroids. Carnforth, UK: Parthenon Publishing, 1999. p. 51–4.

[15] Maruo T, Samoto T, Takeuchi S, Spitz I, Johansson E. Usefulness of levonorgestrel-releasing IUD in the management of menorrhagic women with uterine myoma and adenomyosis. In: Proceedings of the Presentation held at the Xth International Congress of the Society for the Advancement of Contraception, Manila, Philippines, 1998.

[16] D. Wildemeersch, E. Schacht, P. Wildemeersch. Treatment of primary and secondary dysmenorrhea with a novel "frameless" intrauterine levonorgestrel-releasing drug delivery system: a pilot study. Eur. J. Contraception, Reprod. Health Care, submitted for publication.

[17] Sturridge F, Guillebaud J. A risk-benefit assessment of the levonorgestrel-releasing intrauterine system. Drug Safety Dec 1996;15(6):430–40.