

Performance and acceptability of intrauterine release of levonorgestrel with a miniature delivery system for hormonal substitution therapy, contraception and treatment in peri- and postmenopausal women

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Abstract

Objective: To evaluate the performance and acceptability of a novel intrauterine drug delivery system, FibroPlant-levonorgestrel (LNG), derived from the frameless GyneFix intrauterine device, in 141 perimenopausal and postmenopausal women. The trial is an extension of an earlier conducted pilot study. *Design:* A 1-year non-comparative prospective clinical trial. *Subjects:* The treatment with the FibroPlant-LNG intrauterine system (IUS) was instituted to establish a smooth transition to menopause and suppress the endometrium during estrogen substitution therapy (EST) to prevent endometrial proliferation and bleeding. Also women with heavy or postmenopausal bleeding, and women needing contraception, were included in the study. The majority of peri- and postmenopausal women received percutaneous 17 β estradiol (Oestrogel), 1.5 mg daily on a continuous basis, which provides sufficient blood levels of estrogen in most women to suppress climacteric symptoms and protection against bone loss. *Outcome measures:* The clinical results and ultrasonographic effect of this new intrauterine progestin delivery system. A 4-cm long coaxial fibrous delivery system, delivering approximately 14 μ g/day of levonorgestrel (LNG) was used. The calculated duration of release of the system is at least 3 years. *Results:* Eighty-three insertions were done in perimenopausal women with age between 44 and 64, and 58 in postmenopausal women with age between 43 and 73. Over 90% were followed-up for at least one year (range 8-38 months). Fifty-one perimenopausal women received the IUS for contraception in addition to EST. There were no pregnancies reported in the study. Of the total group of 141 women, 108

women maintained or developed amenorrhoea, 52 or 63.5% of the perimenopausal and virtually 100% of the postmenopausal women, respectively, with occasional spotting requiring panty liner protection or no protection in the latter women. Twenty-one perimenopausal women (25.6%) had strongly reduced regular menstruations without spotting. Seven women (8.5%) complained of significant irregular bleeding which resulted in 3 of the 4 removals in the study. In one of them a large polyp (2.5 cm in diameter) was removed. Eleven women with heavy bleeding (5 of them with single or multiple intramural and subserosal fibroids (3-6 or cm or more with no evidence of submucosal fibroids) were all successfully treated, except one. All women with hyperplasia (6 simple and 2 atypical adenomatous hyperplasia) were treated effectively as confirmed by endometrial biopsy performed at least 12 months following treatment initiation.

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

The study with total number of 1432 women-months of use was well followed-up. Only 3 women (2.4%) were lost for final analysis. Ninety-three percent of women are continuing to use the method. *Conclusion:* The results of this study in perimenopausal and postmenopausal women suggest that the frameless FibroPlant-LNG IUS is safe, well tolerated and effective in suppressing the endometrium during EST. The small insertion tube (3.8 mm) allows easy passage through the cervix in virtually all women. FibroPlant-LNG IUS is a highly satisfactory mini-dose treatment with a high continuation of use. The fact that the IUS also acts as a contraceptive, and significantly reduces menstrual bleeding, as demonstrated in earlier studies, is of added importance. The optimal time to initiate the substitution therapy is during perimenopause when women are likely to consider ongoing treatment. FibroPlant-LNG IUS could then contribute to maximise the long-term health benefits of HST.

Keywords: Intrauterine drug delivery system (IUS), levonorgestrel, hormone substitution therapy, contraception, menorrhagia, hyperplasia.

Introduction

The perimenopause is the period of physiological change surrounding the final menstruation in women's life and is characterized by a decline in ovarian function and estrogen/progesterone deficiency symptoms, including vasomotor symptoms and menstrual bleeding disorders. The postmenopause follows the perimenopause and starts 12 months after the last menstrual period.¹ The ovarian function during the perimenopausal phase is not absent as it is mostly in postmenopause.² This decline is unpredictable in time and has been estimated to occur approximately 2-8 years before menopause.^{3,4} Up to 90% of women may experience menstrual changes during the transition to menopause.⁵ Abnormal uterine bleeding is the most frequent gynecological complaint in the perimenopause and the incidence increases as the woman approaches menopause.^{6,7} Heavy menstrual bleeding occurs frequently. The bleeding is often menorrhagic and is, therefore, an important reason for hysterectomy in the perimenopause.⁸ Heavy bleeding is caused by dysfunction of the corpus luteum in approximately half of perimenopausal women as no significant uterine pathology could be demonstrated in 50% among them.⁹ Consequently, there is a risk for endometrial hyperplasia and endometrial cancer due to the decline in luteal phase progesterone excretion. Although there is a reduced frequency of ovulation in the perimenopause, contraception is still necessary. Unplanned pregnancies and induced abortions are frequent in women over the age of 40 and are second only to unintended pregnancies in adolescents in the USA.¹⁰ The climacteric symptoms, particularly hot flashes, night sweats, sleeping disturbances and depressive moods elicited by the decline in circulating estrogens, can cause considerable distress to women. These are usually more severe in perimenopausal than postmenopausal women. Up to 85% of perimenopausal women report suffering from vasomotor symptoms and their well being is negatively correlated to the frequency of hot flashes.¹¹

Various regimens for hormone substitution are available. One of the major problems with combined oral estrogen/progestogen HST is progestogen induced premenstrual tension (e.g., mood changes, headache, sleepiness, mastalgia, nausea).¹² Also metabolic changes can occur. Progestogens have an essentially anti-estrogenic effect and can potentially counteract the beneficial effects of co-administered estrogens. This is a major concern as the cardioprotective action of estrogens on the arterial physiology, preventing ischemic events, and on the lipid and lipoprotein profile, could be adversely altered by progestogens in a dose and duration dependent manner.^{13,14}

The most obvious approach, at least from a physiological approach, seems to develop a system which releases the progestogen locally in the uterine cavity. This is logical since the major reason for progestogen use in non-hysterectomised women is for endometrial protection against estrogenic hyperstimulation. To minimise unwanted side-effects, the minimum dose to obtain the desired effect, should be used. This is likely to lead to optimal patient compliance.

The levonorgestrel T-shaped intrauterine system (T-LNG IUS), developed by Leiras (Turku, Finland) for contraception, releases 20µg of LNG per day. The T-LNG IUS has also been tested for endometrial protection during estrogen substitution therapy.¹⁵⁻¹⁸ The studies concluded that the T-LNG IUS is a suitable treatment for perimenopausal women to prevent endometrial proliferation induced by estrogen. Problems with fitting and abdominal pain complaints were common especially in postmenopausal women.^{19,20}

The purpose of the development of the "frameless" FibroPlant-levonorgestrel (LNG) intrauterine system (IUS) is to provide a miniature, well tolerated, drug delivery system releasing a low dose of LNG sufficient for endometrial suppression in peri- and postmenopausal women and to avoid systemic effects.

Preliminary clinical studies with the FibroPlant-LNG IUS in peri- and postmenopausal women, releasing 14 µg of LNG per day, suggest that the IUS is effective to provide strong endometrial suppression during estrogen substitution therapy.²¹ Preliminary clinical trials have also demonstrated the beneficial effect of the FibroPlant IUS in reducing menstrual blood loss, its efficacy for the treatment of endometrial hyperplasia, and its contraceptive action. These initial clinical trials suggest further that the simple design characteristics of the FibroPlant-LNG IUS account for minimising the occurrence of complaints of pain and expulsion and that the low daily release rate of LNG from the FibroPlant-LNG IUS is responsible for the low incidence of hormonal side-effects.²²

The present study is an extension of a pilot study conducted with the FibroPlant-LNG IUS. The aim of the study was to gain additional clinical experience on the use of the IUS to for endometrial suppression during EST and for the treatment of other gynecological conditions (e.g. menorrhagia, hyperplasia) in peri- and postmenopausal women and for contraception.

Materials and methods

Description of the FibroPlant-LNG IUS

The FibroPlant-LNG IUS and its insertion procedure has been described previously.²¹ In contrast with the T- LNG-IUS, Mirena[®], the FibroPlant-LNG IUS releases only 14 µg/day of LNG instead of 20 µg; it has no frame, is completely flexible, adapting to cavities of every size and shape.

Admission

Perimenopausal women who consulted with climacteric symptoms or menstrual problems, and who still needed contraception, were enrolled in the study. Symptomatic postmenopausal women, using already some form of EST but having side-effects, or who requested treatment for some gynecological condition (e.g., postmenopausal bleeding), were also admitted in the study. To minimise the drop-out rate, great personal attention was given to the candidates to explain the advantages and possible disadvantages of the substitution therapy. Women were told that they could expect scanty inter-menstrual bleeding during the first weeks or months but that this is a normal side-effect which usually disappears in time and should not worry them. The study was approved by the Ethics Committee of the University in Ghent, Belgium. Written informed consent was obtained. Prior to the insertion procedure, a medical history was taken and pelvic examination was carried out and the patient checked for any clinical signs of sexually transmitted diseases. Since women included in the study were at low risk for sexual transmitted diseases (STDs), no routine chlamydia tests were done. All women were screened for their clinical suitability for IUD insertion and compliance with the eligibility criteria. The following were excluded: clinical cervicitis or vaginitis (infection should be ruled out); sound length greater than 10 cm; history of PID, genital actinomycosis or chronic pelvic pain; blood clotting disorder and/or undiagnosed genital tract bleeding; known or suspected uterine or cervical malignancy including unresolved, abnormal PAP smear; congenital malformation of the vagina, cervix or uterus; postpartum endometritis or history of infected abortion; leukemia; currently receiving corticosteroid or immunosuppressive therapy; congenital valvular heart disease. The uterine status was evaluated by transvaginal ultrasound examination prior to insertion of the implant system, and by an endometrial biopsy with a pipelle sampling device when indicated (i.e., abnormal bleeding). In the event that basal and

parabasal cells were found on a wet vaginal smear, indicating an atrophic status of the uterus, EST was started immediately and the insertion of the FibroPlant system was postponed until the uterus was sufficiently primed (usually one month later). This was not necessary in all perimenopausal women included in the study. All insertions were performed in a private practice by the same investigator (DW) and were done without or with local, intracervical, anaesthesia. Insertion of the FibroPlant IUS is identical to the insertion of the GyneFix implant system.

Following insertion, gentle traction on the tail of the IUS was exerted to feel if the anchor was properly fixed. A transvaginal ultrasound (TVU) was performed (Ultramark[®] 4Plus, ATL Inc., USA) to locate the device in the uterus as described previously.²¹

Percutaneous estrogen-containing gel in a dosage of 0.75 to 1.5 mg/day or a transdermal matrix system, in a dosage of 50 µg per day, was used for administering the estrogen.

Follow-up

Women were followed-up at 1, 3, 6, and 12 months following insertion of the IUS and 6-monthly thereafter. They were asked about their bleeding pattern and about any side-effects or adverse reactions. A gynecological examination was performed as well as a transvaginal ultrasound to locate the implant and to evaluate the thickness of the endometrium according to Fleischer and Kepple.²³

Data collection, monitoring and analysis

Data were recorded on standard pre-coded forms at admission, at each scheduled and unscheduled follow-up visit, and upon discontinuation from the study. The cut-off date was 15 July 2001. All data were sent to the data coordinating center at the Department of Medical Informatics and Statistics, University Hospital Gent, Belgium, for providing statistical data analysis for the study. The rates of discontinuation for individual reasons and groups of reasons were analysed using the S-PLUS statistical software package (Mathsoft Corporation)²⁴ and the cumulative discontinuation rates were computed using survival analysis methods.^{25,26}

Results

Between May 1998 and August 2000, the FibroPlant-LNG implant system was inserted in 141 perimenopausal and postmenopausal women.

Eighty-three insertions were done in perimenopausal women with age ranging from 44 to 46 (Table 1). The majority of them were thought to be close to menopause because of their age and the presence of climacteric signs and symptoms. They received the FibroPlant-LNG IUS in addition to estrogen to establish a smooth transition to menopause. Fifty-one women also received the FibroPlant IUS for contraceptive purposes. Forty-two of these women were fitted with FibroPlant-LNG immediately after removal of the GyneFix copper IUD. In three perimenopausal women with abnormal uterine bleeding, endometrial hyperplasia was diagnosed. Two had simple hyperplasia and one atypical adenomatous hyperplasia. Eleven women complained of heavy menstrual bleeding prior to entering the study; in five of them significant uterine fibroids were found. Women treated for excessive bleeding and those who had endometrial hyperplasia, did not receive EST. In case EST was not instituted from the beginning, estrogens were added when vasomotor or other climacteric symptoms appeared.

Fifty-eight insertions were done in postmenopausal women, mainly for endometrial protection during EST. The age of women ranged from 43 to 73 (Table 1). In 5 postmenopausal women, the FibroPlant-LNG IUS was inserted to counteract postmenopausal bleeding which was caused by unopposed estrogen therapy in four of them. One woman had irregular bleeding during adjuvant tamoxifen treatment for breast cancer. In these five women an endometrial biopsy confirmed the diagnosis of simple glandulocystic hyperplasia in four and atypical adenomatous hyperplasia in one patient. Insertion was difficult in two postmenopausal women due to cervical stenosis, necessitating sounding and some dilatation of the cervical canal. In three postmenopausal women small fibroids were present.

Table 1. Characteristics of the 141 FibroPlant-LNG IUS users: Age distribution.

Age (years)	Perimenopausal	Postmenopausal
No	83	58
Mean	45	58
Lowest	44	43
Highest	46	73
Total	141	

The events and cumulative gross discontinuation rates are presented in Table 2. The total use-related discontinuation rate was low (2.3) and results in a high rate of continuation of use in both perimenopausal (98.8) and postmenopausal women (96.1). Three women (two perimenopausal women and one postmenopausal woman) were lost to follow-up. One of these women could not be traced and the two other women refused to come for follow-up examination probably because of ambiguous feelings about the benefits and risks of EST although they were symptom-free and had normal gynecological examinations at the time of their last visit.

By 15 July 2001, over 90% of women had at least one year follow-up (range 8-38 months).

No pregnancies occurred in the fifty-one perimenopausal women who needed contraception and no FibroPlant-LNG IUS were expelled during the observation period. There were four removals, three for irregular bleeding and one removal for non-medical reasons. In one of these women the presence of a 2.5 cm large benign endometrial polyp, diagnosed by TVU, caused irregular bleeding and resulted in removal of the polyp by hysteroscopy.

Fifty-two of the perimenopausal women developed amenorrhoea during treatment. Seven women complained of scanty erratic bleeding which resulted in the three medical removals mentioned above. Twenty-one of the perimenopausal women had regular but scanty menstrual periods requiring mostly a panty liner for protection. Of the eleven women complaining of heavy bleeding before treatment, of whom five had significant fibroids, only one woman in this group was not treated successfully and resulted in removal of the IUS. One other woman in the 'heavy bleeding' group responded only after 6 months. Four of the five women with fibroids experienced a significant reduction in amount of menstrual blood loss.

All fifty-six postmenopausal women remaining in the study were amenorrhoeic at the cut-off date, including the three women treated for endometrial hyperplasia. One postmenopausal woman underwent hysterectomy for a para-ovarian tumor and one IUS was removed for non-medical reasons 6 months after the start of the treatment, non-related to the use of the trial product.

Table 2. Events and cumulative gross discontinuation rates per 100 women in 141 FibroPlant-LNG users.

	Perimenopausal		Postmenopausal		All data	
	No.	Rate \pm SD	No.	Rate \pm SD	No.	Rate \pm SD
Pregnancy	0	0	0	0	0	0
Expulsion	0	0	1	0	1	0
Removal for medical reasons	4	1.2 (0, 3.6)	1	1.9 (0, 5.7)	5	1.5 (0.3, 3.6)
Removal for non- medical reasons	0	0	1	2.0 (0, 5.9)	12	0.8 (0.2, 3.2)
Removal for 'other reasons'	0	0	0	0	0	0
Total use-related discontinuation	4	1.2 (0, 3.6)	3	3.9 (0, 9.2)	7	2.3 (0, 4.8)
Loss to follow-up	2	3.1 (0, 7.3)	1	0	3	1.9 (0, 4.6)
Continuation rate	77	98.8	54	96.1	131	97.7
Women recruited	83		58		141	
Women-months of use	875		753		1432	

All perimenopausal and postmenopausal women with amenorrhoea had a thin endometrium (< 5 mm in thickness), as assessed by transvaginal ultrasound (Figure 2). Those women who still menstruated developed a thin endometrium almost indistinguishable from the endometria observed on ultrasound in the peri- or postmenopausal women with amenorrhoea. No hormonal side-effects were reported. Slight scanty and infrequent bloody discharge requiring no protection, or a small panty liner, occurred in the majority of women during the first weeks of treatment, usually for a very short duration in postmenopausal women and those close to menopause. In eight women, this erratic, blood-stained, discharge lasted longer. However, only three removals were performed for that reason, all of them in perimenopausal women of whom one had a large endometrial polyp, as mentioned previously. Neither severe adverse reactions (e.g., pelvic inflammatory disease, perforation) were recorded, nor complaints of abdominal pain by users of the FibroPlant-LNG system. One hundred and thirty-one women (97.7%), which includes the three women who did not return for follow-up, are continuing to use the method and are free of side-effects.

Discussion

The majority of women take hormone substitution therapy to obtain relief from climacteric symptoms rather than for prevention of cardiovascular disease or osteoporosis. Climacteric symptoms are most distressing during the perimenopausal years. In Western societies, a high percentage of perimenopausal women request doctor's advice for that reason and, consequently, the uptake of HST is highest during the transition to menopause. However, 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 HST will continue it for more than a year.²⁷⁻³⁰ Reinitiation of bleeding, breakthrough bleeding and hormonal side-effects, caused by systemic progestogen absorption, are usually the reason for discontinuing the therapy. If these women can be offered a non-systemic progestogen method, with the concomitant advantage of providing contraception and treatment of heavy bleeding, if present, satisfaction with the method is likely to be significantly enhanced. Hormonal side-effects and abnormal bleeding are the most important symptoms to avoid as they will determine if the woman will continue the method or not. It appears to us, therefore, that optimal patient compliance will only be obtained if these factors are fully dealt with. These privileged women will then be able to receive the full impact of HST's preventive health benefits.

With conventional estrogen-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 major reason to discontinue the method in over 30% of women.¹² Continuous combined HST has been developed to cause amenorrhoea by inducing endometrial atrophy. This treatment regimen has been called "bleed-free" but for many patients this is a wrong denomination. Higher doses of progestogen might help in reducing these irregular bleedings but this increases side-effects and metabolic consequences due to the higher progestogen levels.³¹ In long-cycle HST, 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.³² The duration of the progestogen administration seems more important than the daily dose as far as prevention of endometrial hyperplasia is concerned.³³ These treatments are, therefore, unsuitable for many women during the perimenopause and within 12 months of the last menstrual period.¹²

At the start of the present study 82 women were perimenopausal and 59 postmenopausal. The intrauterine delivery of low-dose LNG maintained or established amenorrhoea in all postmenopausal and in the majority of perimenopausal women. Spotting episodes occurred rarely after amenorrhoea was established. Previous studies with the T-LNG IUS have shown that a continuous exposure to LNG results in a uniform suppression of the endometrium as soon as one month after treatment initiation and remains constant during prolonged use.³⁴ This has been confirmed in a pilot study with the FibroPlant-LNG IUS in perimenopausal and

postmenopausal women.²¹ Although the bleeding pattern in the present study was not statistically evaluated separately, the low-dose 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.¹⁹ The attention given to the subject in the study may have contributed to the low removal rate for that reason. It remains unanswered why some women, using combined continuous HRT with intrauterine LNG, after a long period of amenorrhoea, suddenly experience short episodes of spotting. A way to avoid bleeding disturbances during the initial months following the insertion of the IUS would be to administer a low dose of estrogen from the beginning to induce endometrial tissue repair of the progestogen-induced defects in the overlying endometrium.³⁵ Also insertion of the IUS within 7 days following the initiation of menstruation seems to prevent more or less the occurrence of irregular breakthrough bleeding.

Patient satisfaction and continuance depends on the presence or absence of bleeding problems. An optimal long-term compliance can be expected if abnormal bleeding can be minimised. The high incidence of amenorrhoea obtained with the low-dose LNG IUS has been advantageous to women in this study. Sixty-three percent of perimenopausal women became amenorrheic. This is similar to the 61.7% amenorrhoea rate after 2 years reported in studies with the T-LNG IUS in perimenopausal women.¹⁹

Previous studies conducted with the FibroPlant-LNG IUS have also shown a high efficacy in reducing the amount of menstrual bleeding in women with menorrhagia.²² Heavy bleeding is common in the perimenopause. The high efficacy in treating this condition is confirmed in the present study. Except when intrauterine anomalies (e.g., polyps, submucosal fibroids) are present, successful treatment is generally the rule. This treatment could, therefore, be helpful in trying to reduce the number of hysterectomies which is the most common surgical procedure performed in perimenopausal women.³⁶

Successful treatment of endometrial hyperplasia, a frequent condition in peri- and postmenopausal women, has been demonstrated with the FibroPlant-LNG IUS in 12 women with endometrial hyperplasia.³⁷ The treatment was effective in simple hyperplasia as well as in adenomatous hyperplasia without or with cellular atypia as confirmed by repeat endometrial biopsy 12 months after treatment initiation. Other studies conducted in women

with simple and atypical endometrial hyperplasia, treated with the T-LNG IUS, came to the same conclusion.^{38,39}

Transvaginal ultrasound evaluation, as used in this study, is a non-invasive technique which is very useful in the evaluation of the endometrium. In a study by Fleischer et al. the correlation of the ultrasound appearance of the endometrium with histopathological findings was found to be reliable.⁴⁰ Ultrasound appears, therefore, a sensitive screening method and indicates the need for endometrial biopsy. The latter can be avoided in many women when the mid-line echo is narrow. This approach was followed to monitor the endometrium in the present study.

The FibroPlant system is a further development of intrauterine drug delivery systems exploiting the benefits of the atraumatic frameless design, which minimizes the side-effects and discomforts which peri- and postmenopausal women may experience with conventional IUDs and current intrauterine steroid delivery systems due to incompatibility.^{19,20} Peri- and postmenopausal women often have small uterine cavities which can gradually reduce in size due to the suppressive effect of the LNG.

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 contraceptive effect of locally administered LNG is highly desirable as many perimenopausal women run considerable risk of unintended pregnancy.⁴¹ Intrauterine drug delivery may, therefore, constitute a welcome reversible alternative to other contraceptive options which may be less suitable at this age.

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References

1. World Health Organization Scientific Group (WHO) 1996 Research on the Menopause in the 1990s. WHO Technical Services Report Series No. 866, Geneva: World Health Organization.
2. Nilsson L. The hormonal situation in the perimenopausal period. *Acta Obstet Gynecol Scand* 1985; Suppl 130:9-11.
3. McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. *Maturitas* 1992;14:103-115.
4. Burger HG. Pituitary and ovarian changes. In *Estrogens and Progestogens in Clinical Practice*, ed. IS Fraser, RPS Jansen, RA Lobo and MI Whitehead, pp. 627-634, Churchill Livingstone, London, 1998.
5. Bachman GA. The change before the "change": Strategies for transition to the menopause. *Postgrad Med* 1994;113-124.
6. Santoro N, Rosenberg-Brown J, Adel T, Skurnick JH. Characterization of reproductive hormonal dynamics in the perimenopause. *J Clin Endocrinol Metab* 1996;81:1495-1501.
7. Nesse RE. Abnormal vaginal bleeding in perimenopausal women. *Am Fam Phys* 1989;40:185-192.
8. Hallberg L, Högdahl A, Nilsson L, Rybo G. Menstrual blood loss - a population study. *Acta Obstet Gynecol Scand* 1966;45:330-351.
9. Rybo G. Population studies of menorrhagia. *Research and Clinical Forums* 1983;5:77-81.
10. Henshaw SK. Unintended pregnancy in the United States. *Fam Plann Perspect* 1998;30:24-29.
11. Brzechffa PR, Judd HL. Hot flashes. In *Estrogens and Progestogens in Clinical Practice*, ed. IS Fraser, RPS Jansen, RA Lobo and MI Whitehead, pp. 635-645, Churchill Livingstone, London, 1998.
12. Whitehead MI. General principles of administration of hormone replacement therapy: indications and contraindications, routes of administration, treatment schedules. In *Estrogens and Progestogens in Clinical Practice*, ed. IS Fraser, RPS Jansen, RA Lobo and MI Whitehead, pp. 667-686, Churchill Livingstone, London, 1998.
13. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature* 1980;288:373-376.
14. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, Vittinghoff E for the Heart and Estrogen/progestin Replacement Study (HERS) Research Group. Randomized Trial of

- Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women. *JAMA* 1998;280:605-613.
15. Andersson K, Mattsson LA, Rybo G, Stadberg E. Intrauterine release of levonorgestrel - a new way of adding progestogen in hormone replacement therapy. *Obstet Gynecol* 1992;79:963-967.
 16. Raudaskoski TH, Lahti EI, Kauppila AJ, Apaja-Sarkkinen MA, Laatikainen TJ. Transdermal estrogen with levonorgestrel-releasing intrauterine device for climacteric complaints: clinical and endometrial responses. *Am J Obstet Gynecol* 1995;172:114-117.
 17. Suhonen SP, Allonen HO, Lähteenmäki P. Sustained-release estradiol implants and a levonorgestrel-releasing intrauterine device in hormone replacement therapy. *Am J Obstet Gynecol* 1995;172:562-567.
 18. Suhonen SP, Allonen HO, Lähteenmäki P. Three-year follow-up of the use of a levonorgestrel-releasing intrauterine system in hormone replacement therapy. *Acta Obstet Gynecol Scand* 1997;76:145-150.
 19. Boon J. The LNG intrauterine system as part of continuous combined HRT in perimenopausal women. Dissertation, University Utrecht, Faculty of Medicine, The Netherlands, 1998.
 20. Birkhäuser MH. New routes of HRT administration. *Int J Fert* 1998;43:206-207.
 21. Wildemeersch D, Schacht E. Endometrial suppression with a new "frameless" levonorgestrel releasing intrauterine system in perimenopausal and postmenopausal women: a pilot study. *Maturitas* 2000;36:63-68.
 22. Wildemeersch D. Development of a miniature, frameless intrauterine levonorgestrel-releasing intrauterine system for contraception and treatment: a review of clinical experience. *Reproductive BioMedicine* 2002;4:69-80.
 23. Fleischer AC and Kepple DM. Benign conditions of the uterus, cervix and endometrium. In *Transvaginal ultrasound*, ed. DA Nyberg, LM Hill, M. Böhm-Velez, and EB Mendelson, pp. 21-24, Mosby Year Book, St Louis, 1992.
 24. SAS Institute Inc. *SAS User's Guide: Basics, Version 5 Edition*. Cary, NC: SAS Institute Inc. 1985.
 25. Tietze C, Lewit S. Recommended procedures for the statistical evaluation of intrauterine contraception. *Stud Fam Plann* 1972;4:35-42.
 26. Farley TMM. Life-table methods for contraceptive research. *Statistics in Medicine* 1986; 5:475-489.

27. Hammond CB. Women's concerns with hormone replacement therapy - compliance issues. *Fertil Steril* 1994;62S2:157S-160S.
28. Hill DA, Weiss NS, La Croix AZ. Adherence to postmenopausal hormone therapy during the year after the initial prescription: A population-based study. *Am J Obstet Gynecol* 2000;182:270-276.
29. Castelo-Branco C, Figueras F, Sanjuan A, Vincente JJ, Martinez de Osaba MJ, Pons F, Balasch J, vanrell JA. Long-term Compliance with Estrogen Replacement Therapy in Surgical Postmenopausal Women: Benefits to Bone and Analysis of Factors Associated with Discontinuation. *J North Am Menopause Soc* 1999;6:307-311.
30. Ettinger B, Pressman A, Silver P. Effect of Age on Reasons for Initiation and Discontinuation of Hormone Replacement Therapy. *J North Am Menopause Soc* 1999;6:282-289.
31. Magoo AL, Brincat M, Studd JWW, Wardle P, Schlesinger P, O'Dowd T. Amenorrhoea and endometrial atrophy with continuous oral estrogen and progestogen therapy in postmenopausal women. *Obstet Gynecol* 1985;65:496-499.
32. Cerin A, Heldaas K, Moeller B. Adverse endometrial effects of long-cycle estrogen and progestogen replacement therapy. *New Engl J Med* 1996;334:668-669.
33. Whitehead MI, Hillard TC, Crook D. The role of progestogens. *Obstet Gynecol* 1990;75:29S-76S.
34. Silverberg SG, Haukkamaa M, Arko H, Nilsson CG, Luukkainen T. Endometrial morphology during long-term use of levonorgestrel-releasing intrauterine devices. *Int J Gynecol Path* 1986;5:235-241.
35. Smith SK. The pathophysiology of menstruation. In *Clinical disorders of the endometrium and the menstrual cycle*, ed. IT Cameron, IS Fraser and SK Smith, pp. 105-115, Oxford University Press, Oxford, 1998.
36. Voda AM, Kernoff Mansfield P, Root JL. Menstruation, surgery, and women. In *Clinical disorders of the endometrium and the menstrual cycle*, ed. IT Cameron, IS Fraser and SK Smith, pp. 67-85, Oxford University Press, Oxford, 1998.
37. Wildemeersch D, Schacht E, Wildemeersch P. Treatment of hyperplasia with a new "frameless" levonorgestrel releasing intrauterine system: a pilot study. *Maturitas* 2001 (submitted).
38. Perino A, Quartararo P, Catinella E, Genova G, Cittadini E. Treatment of endometrial hyperplasia with levonorgestrel releasing intrauterine devices. *Acta Europaea Fertilitatis* 1987;18:137-140.

39. Scarcelli G, Tantini C, Colafranceschi M, Taddei GL, Bargelli G, Venurini N, Branconi F. Levonorgestrel-Nova-T and precancerous lesions of the endometrium. *Eur J Gynaec Oncol* 1988;9:284-286.
40. Fleischer AC, Kalemeris GC, Machin JE, Entman SS, James AE. Sonographic depiction of normal and abnormal endometrium with histopathologic correlation. *J Ultrasound Med* 1986;5:445-452.
41. Grimes D. Contraception for women in the perimenopause. In *The Contraception Report* 2001;2001:4-12.

FIGURES

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



Figure 2. Ultrasound picture of FibroPlant-LNG in situ. The metal clip is highly visible allowing proper location of the IUS (S-S distance 15 mm). The endometrium is atrophic.



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