6

# From Heavy Menstrual Bleeding to Amenorrhoea and Reversal of Anaemia - Novel, Effective, Intrauterine Levonorgestrel-Releasing Systems for Contraception and Treatment

D. Wildemeersch[1] and A. Andrade[2]
[1]*Outpatient Gynaecological Clinic and IUD Training Center, Ghent*
[2]*Centro de Biologia da Reprodução, Universidade Federal Juiz de Fora, Juiz de Fora*
[1]*Belgium*
[2]*Brazil*

## 1. Introduction

Menorrhagia, defined as regular but heavy menstrual bleeding of more than 80 ml from a secretory endometrium is a common disorder. The prevalence is between 9% and 28% of women aged 16-45 years and increases with age.[1] Approximately 30% of patients referred for gynaecological treatment are for menorrhagia and half of these women have a hysterectomy within 5 years if conservative treatment (e.g. contraceptive pills, progestogens, fibrinolytic inhibitors and prostaglandin inhibitors) fails. More than one third of these women undergoing hysterectomy have normal uteri.[2,3]

In the USA, more than 600,000 hysterectomies are performed each year of which 30% 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 menorraghia 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.[4]

When menstrual blood loss exceeds 80 ml, the incidence of anaemia (haemoglobin less than 12 g/dl) is increased significantly.[5] Anaemia is one of the most widespread, and most neglected, nutritional deficiency diseases in the world today.[6] 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 causing severe social embarrassment and repudiation by the partner.

In recent years, new less invasive treatment options have been developed.[7] Endometrial ablation techniques and classical endometrial resection have their value but are costly although significantly cheaper than hysterectomy. They are also irreversible. Second generation endometrial ablation techniques have fewer complications, are quicker and they seem to be more suitable for local anaesthesia than the first generation techniques.

The intrauterine system releasing 20 µg of levonorgestrel (Mirena® LNG-IUS) has shown a dramatic decrease in menstrual blood loss in nearly all women and amenorrhoea in up to 20% or more due to profound endometrial atrophy.[8,9,10]

The present report reviews the reduction of menstrual flow following insertion of the Femilis® LNG-IUS, a new T-shaped hormone-releasing IUS, releasing 20 µg of LNG/day. The report also evaluates other menstrual blood loss (MBL) studies, using the same drug delivery technology for the release of LNG, in which the effect on MBL was assessed with a frameless LNG-IUS, releasing only 14 µg of LNG/day, instead of 20 µg of LNG/day with the framed LNG-IUS. The evaluation is based on 6 clinical studies of which most of them were reported elsewhere.[11,12,13,14,15] The use of the LNG-IUS as first option treatment of menorrhagia or heavy menstrual bleeding is discussed, including for the treatment of iron deficiency anaemia.

## 2. Materials and methods

### 2.1 Description of the T-LNG (Femilis®) IUS (Fig. 1) and the frameless FibroPlant®-LNG IUS (Fig. 2)

The T-LNG-IUS (Femilis®, Contrel Drug Delivery Research, Belgium) has a 3-cm long and 2.4-mm wide fibrous delivery system, consisting of a LNG-ethylene vinyl acetate (EVA) core and an EVA rate-controlling membrane that releases approximately 20 µg of LNG daily. The drug compartment is provided with a crossarm fixed to the upper part of the drug delivery rod. The total length of the crossarm is 28 mm. The polyethylene crossarm contains 22% barium sulphate to render it radiopaque. The single tail is made of a 00 gauge polypropylene.

Fig. 1. Femilis®

The FibroPlant® LNG-IUS (Contrel Drug Delivery Research, Belgium) 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.

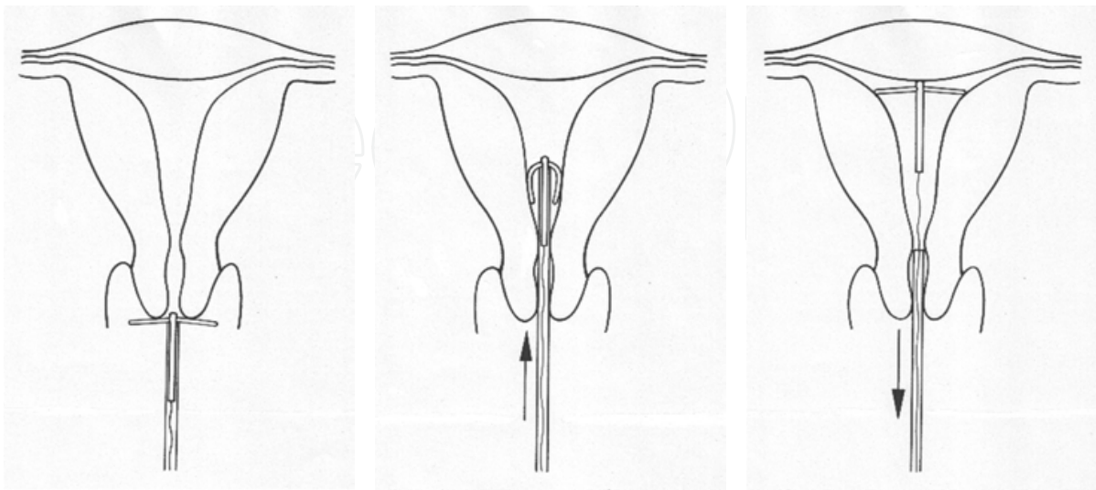
Fig. 2. FibroPlant®

In vitro studies show that the rate of LNG-release is constant over several years (zero-order), except for the first two months of use, and is similar to the in vitro release rate of the Mirena® LNG-IUS. The duration of release is at least five years with the Femilis® LNG-IUS and at least three years with the FibroPlant® LNG-IUS. The in vitro release studies and other pharmacological analyses were conducted in collaboration with the Polymer Research Group, Department of Chemistry, University of Ghent, Ghent, Belgium and with the Analytical Pharmaceutical Chemistry of the Department of Pharmacy, University of Liège, Belgium.

### 2.2 Insertion technique (Fig. 3 and Fig. 4)

**Femilis®**

The T-LNG-IUS (Femilis®) is inserted using the 'push-in' technique. Notably, upon entering the uterine cavity the crossarm unfolds immediately, thus minimising the risk of perforation.



Step 1 Step 2 Step 3

Fig. 3. Insertion procedure of Femilis®.

**FibroPlant®**

The anchoring knot at the proximal end of the thread is implanted into the myometrium of the uterine fundus using the standard GyneFix® insertion technique, thus permanently securing the implant in the uterine cavity. The stainless steel metal clip allows ultrasound and X-ray visibility of the system thus enabling correct location of the system in the uterine cavity, both at insertion and at follow-up. The fibrous delivery system is also visible on ultrasound.
When compared with "framed" drug delivery systems such as the Mirena® and Femilis® LNG-IUS, the FibroPlant® LNG-IUS will be seen to have no frame. It is, therefore, completely flexible, with the ability to adapt to uterine cavities of every size and shape.

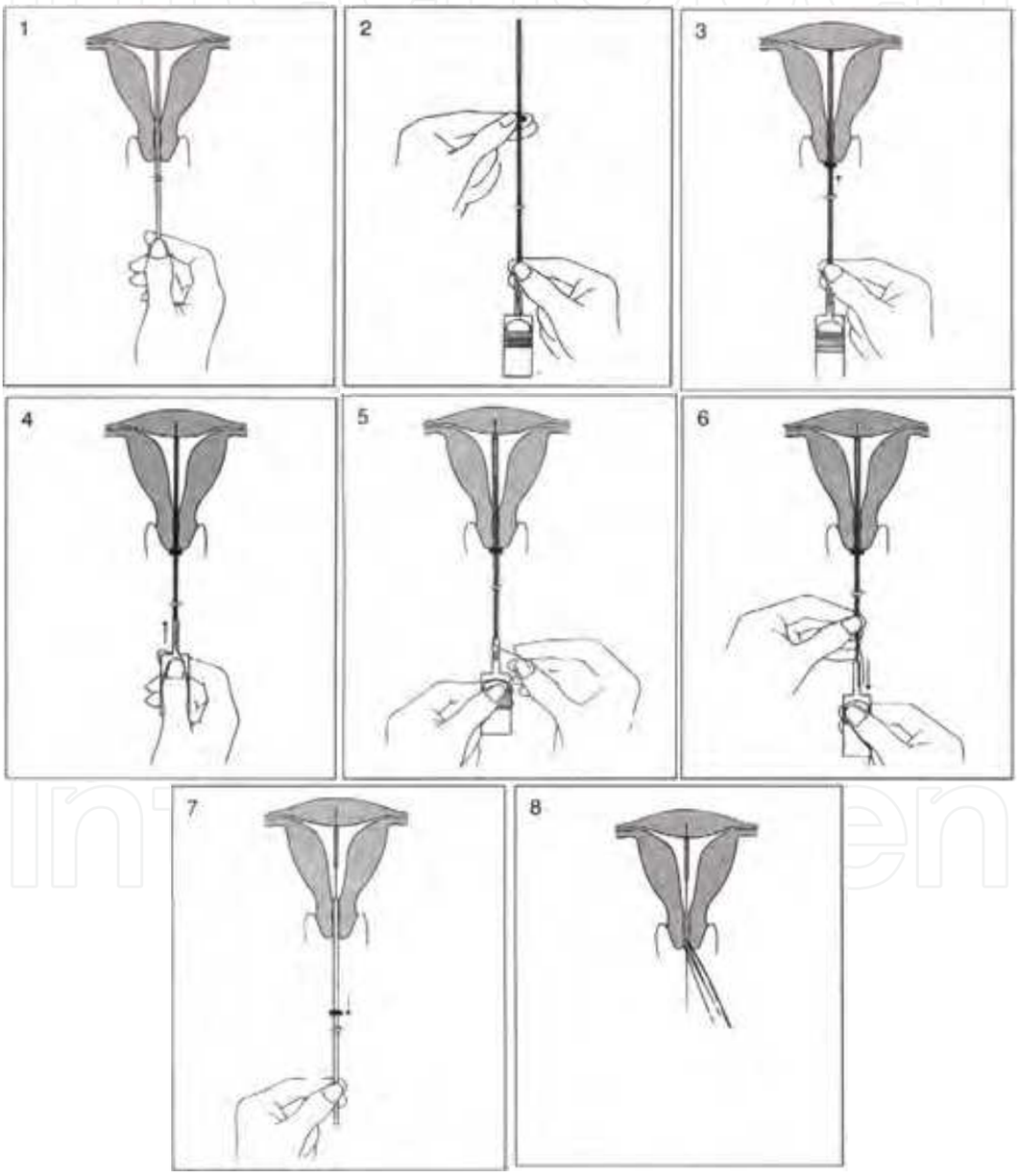



Fig. 4. Insertion procedure of FibroPlant® is identical with the insertion procedure of the frameless GyneFix® copper-releasing IUD (See video insertion on www.wildemeersch.com).

### 2.3 Study population and menstrual blood loss assessment techniques

Study 1: Femilis® in women with and without idiopathic menorrhagia (assessed by the visual menstrual score technique): Women less than 48 years of age at study enrollment with normal and with heavy menstrual periods were admitted into the study. Women with significant fibromyomas (>3 cm), or other uterine pathology, were excluded form the study. Women were followed-up for at least 12 months.

A visual assessment technique was used as described by Janssen.[3] Information on menstrual bleeding was obtained by interview retrospectively using a pictorial chart 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 one, five and 20 for pads and one, 5 and 10 for tampons, respectively, according to their degree of staining (Fig. 5). The visual assessment technique does not yield an exact flow in ml, but, in practice, the sensitivity and specificity is reasonably high and superior to a women's subjective assessment of MBL. For purposes of evaluating the effect of treatment, the visual assessment technique is highly practical compared with the quantitative method, described below, as women no longer have to submit sanitary wear to the laboratory.

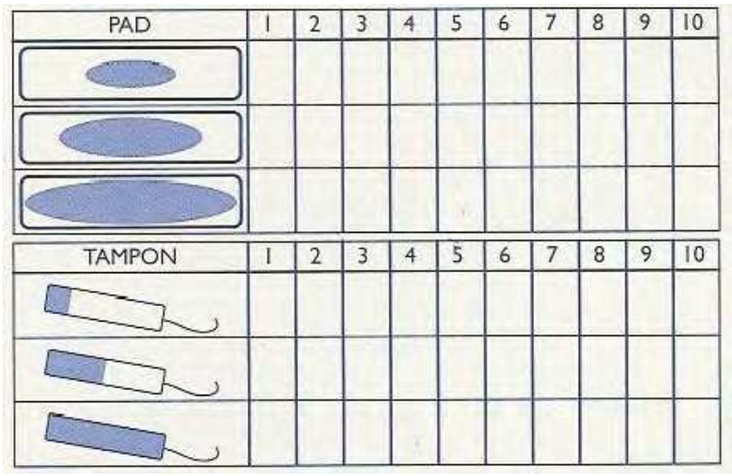



Fig. 5. Pictorial chart for the evaluation of menstrual blood loss.

Study 2: Femilis® in women with and without heavy menstrual bleeding (HMB) (assessed by the quantitative alkaline haematin technique): 14 Brazilian women participated in this menstrual blood loss study (ongoing study). In this study, 6 months results are available in 13 of them. MBL was quantified according to the technique first described by Hallberg and Nilsson[16], adapted by Shaw[17] and modified by Newton[18] before insertion (baseline controls) of the IUS and after 3, and 6 months. Women were instructed to carefully collect their menstrual tampons and bring them to the laboratory in opaque plastic bags as soon as bleeding ended, as described previously.[19] Serum ferritin was also measured at the same intervals as above.

Study 3: FibroPlant® LNG-IUS in women with normal and heavy menstruation (assessed by the quantitative alkaline haematin technique): Menstrual blood loss studies were conducted in 40 Brazilian FibroPlant® LNG users with normal and heavy menstrual bleeding. Women were followed-up for at 3, 6, 12 and 24 months. MBL was quantified according to the technique described above. Serum ferritin was also measured at the same intervals as above.

Study 4: FibroPlant® LNG-IUS in women with idiopathic menorrhagia (visual menstrual score technique): The efficacy of the FibroPlant® LNG-IUS in reducing menstrual blood loss was tested in 12 Belgian women between 17 and 43 years of age suffering from idiopathic menorrhagia using the visual bleeding score (score >185) as described above. Women were followed-up for one year.
Study 5: FibroPlant® LNG-IUS in women with idiopathic menorrhagia (visual menstrual score technique): Thirty-two insertions were performed in fertile women between 31 and 51 years of age for the treatment of menorrhagia as well as for contraceptive purposes. Fifteen women were fitted with the FibroPlant® LNG-IUS immediately following removal of a copper-bearing IUD, the GyneFix® IUD, who developed excessive bleeding. To discriminate between menorrhagia and normal menstrual blood loss, women were evaluated using the visual assessment technique. The trial covers a period from a minimum of 1 month up to 23 months.
Study 6: FibroPlant® LNG-IUS in women with menorrhagia associated with intrauterine fibroids (visual menstrual score technique): Fourteen insertions were performed in premenopausal women between 39 and 48 years of age for the treatment of menorrhagia in the presence of uterine fibroids. The effect on menstrual blood loss was evaluated using the visual assessment technique. Women were followed-up for at least 12 months.
The use of the LNG-releasing IUS was approved by the Ethics Committee of the University of Ghent, Belgium and written informed consent was obtained. The quantitative MBL studies were approved by the Ethics Committee of the University of Juiz de Fora, Brazil. Prior to the insertion procedure, a medical history was taken and pelvic examination was carried out and the patient was checked for any clinical signs of sexually transmitted diseases. A transvaginal ultrasound examination was conducted to check for uterine pathology. In the fibroid MBL study (Study 6), the uterine 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.
Following insertion, a transvaginal ultrasound (TVU) was performed to locate the device in the uterus. An admission form was completed.

### 2.4 Follow-up

Women were followed-up at 1, (3), 6, and 12 months following insertion of the LNG-IUS and six-monthly or yearly thereafter. They were asked about their bleeding patterns and about side effects or adverse reactions. A gynaecological examination was performed as well as a transvaginal ultrasound to locate the device. A follow-up form was completed.

### 2.5 Data collection, monitoring and analysis

Data were recorded on standard pre-coded forms at admission, at each scheduled and unscheduled follow-up visit, and upon discontinuation from the study. All data were sent to

the data-coordinating centre at the Department of Medical Informatics and Statistics, University Hospital, Ghent, Belgium, for statistical data analysis, except the quantitative menstrual blood loss studies which was analysed at the Department of Statistics, Centro de Biologia da Reprodução, Universidade Federal Juiz de Fora, Brazil.

The statistical significance in the studies using the visual assessment technique was calculated according to the *Wilcoxon's Signed Rank test*, $p<0.05$ denoting significance.

In the quantitative MBL study, all comparisons were made by means of the *Chi-square test or the Student's t-test*, $p<0.05$ indicating significance. The coefficient of correlation was used to determine the strength of the relationship between the pairs of variables.

The statistical significance in the studies using the visual assessment technique was calculated according to the *Wilcoxon's Signed Ranks test*, $p<0.05$ denoting significance.

## 3. Results

Study 1: Femilis® LNG-IUS in women with and without idiopathic menorrhagia assessed by the visual menstrual score technique: The trial covers a period from a minimum of four months to more than 30 months of IUS use. MBL scores dropped significantly during the observation period in all women except one. The median menstrual score at baseline in women with normal menstrual bleeding (score <185) was 140 (range 80-160) and dropped to a median score of five (range 0-150) at the last follow-up, a decrease of 96%. In women with hemorrhagic bleeding (score ≥185) at baseline, menstrual flow dropped from a median score of 232 (range 185-450) at baseline to a median score of three (range 0-50) at the last follow-up visit, a decrease of 99%. Twenty women developed amenorrhoea (33%), 10 in the group of women with normal menstruation and 10 in those women with menorrhagia. Most of the remaining women had strong oligomenorrhea requiring the use of a few panty-liners only. In one woman, MBL did not decrease for any apparent reason, thus requiring further evaluation (Table 1).

| | Total (n=60) | | Normal menses (n=28) | | Menorrhagia (n=32) | |
|---|---|---|---|---|---|---|
| | MS at insertion | MS at last follow-up | MS at insertion | MS at last follow-up | MS at insertion | MS at last follow-up |
| Median | 200 | 5 | 140 | 5 | 232 | 3 |
| SD | 87.5 | 21.5 | 25.7 | 29.8 | 75.7 | 9.4 |
| Minimum | 80 | 0 | 80 | 0 | 185 | 0 |
| Maximum | 450 | 150 | 160 | 150 | 450 | 50 |

Wilcoxon matched-pairs signed-rank test: $p<0.001$ (highly significant).

Table 1. Visual menstrual bleeding scores (MS) before and during treatment (observation from 4 months to 31 months) in 60 Femilis users (all women)

Study 2: Femilis® in women with and without heavy menstrual bleeding (HMB) assessed by the quantitative alkaline haematin technique)(ongoing study): Menstrual blood loss reduced from a mean baseline menstrual volume of 47.6 ml to a mean volume of 1.1 ml after 6 months. Ferritin values increased from a mean value of 74.6 ng/ml at baseline controls to a mean level of 93.5 ng/ml after 6 months of use. Amenorrhoea occurred in all women after 6 months of use, except in one woman (Table 2).

| | **MBL** mean (N) | **FERRITIN** mean (N) |
|---|---|---|
| Baseline controls | 47.6 (14) | 74.6 (14) |
| Interval 6 months | 1.1 (13) | 93.5 (13) |

MBL - in ml Ferritin - in ng/ml
Amenorrhoea: all women, except one.

Table 2. Menstrual blood loss quantification (ml) and serum ferritin levels (ng/ml) in 14 Femilis-LNG users compared with controls (preliminary results; study ongoing)

Study 3: FibroPlant® LNG-IUS in women with normal and excessive menstruation assessed by the quantitative alkaline haematin technique: Quantitative menstrual blood loss studies were conducted in 40 Brazilian FibroPlant® users with normal and heavy menstrual bleeding. Menstrual blood loss reduced from a mean baseline menstrual volume of 29.7 ± 2.2 ml to a mean volume of 1.5 ± 2.8 ml after 24 months. Ferritin values increased from a mean baseline value of 31.1 ± 3.2 ng/ml at baseline controls of the LNG-IUS to a mean level of 72.5 ± 2.1 ng/ml after 24 months of use. Differences in menstrual volume and ferritin levels are highly significant ($p<0.0005$) (Table 3). Amenorrhoea occurred in 80% of women out of 40 after 24 months of use.

| | **MBL** mean ± SD (N) | **HGB** mean ± SD (N) | **FERRITIN** mean ± SD (N) |
|---|---|---|---|
| Baseline controls | 29.7 ± 2.2 (40) | 12.4 ± 0.9 (40) | 31.1 ± 3.2 (40) |
| Interval 3 months | 3.3 ± 3.6 (39)* | 12.5 ± 0.9 (39) | 37.1 ± 2.8 (39)* |
| Interval 6 months | 2.0 ± 3.1 (40)* | 12.5 ± 0.9 (40) | 47.8 ± 2.2 (40)* |
| Interval 12 months | 1.7 ± 2.5 (39) * | 12.4 ± 0.8 (40) | 56.2 ± 2.1 (40) * |
| Interval 24 months | 1.5 + 2.8 (40)* | 12.7 + 1.1 (40) | 72.5 ± 2.1 (40)* |

MBL in ml HGB - Ferritin in ng/ml
* $p<0.0005$ Observation: due to skewed distribution MBL and Ferritin values were log transformed before calculations
Amenorrhoea (months): 3: 18 users = 45%; 6: 27 users = 67.5%; 12: 28 users = 70%; 24: 32 users = 80%
MBL: pre-insertion: mean 29.7 ± 2.2ml (variation: 3.6 – 90.0 ml)
At 24 months: mean 1.5 ± 2.8ml (variation: 0 – 29.7ml)

Table 3. Menstrual blood loss quantification (ml) and serum ferritin levels (ng/ml) in 40 FibroPlant-LNG users compared with controls

Study 4: FibroPlant® LNG-IUS in women with idiopathic menorrhagia assessed by the visual menstrual score technique: The results are presented in Table 4. All women reported a marked reduction in menstrual blood loss which started from the first menstrual period following insertion of the IUS. Bleeding reduced further over the next months until the 6$^{th}$ month. No amenorrhoea occurred. The difference in menstrual bleeding was highly significant ($p=0.002$) which resulted in a significant increase in ferritin levels ($p=0.002$).

| | Before insertion | at 12 months |
|---|---|---|
| Median MS ± SD | 325.0 ± 122.2 | 12.5 ± 42.8* |
| Mean ferritin level ± SD | 19.8 ±10.1 | 44.5 ± 22.2* |

Wilcoxon matched-pairs signed-ranks test: *p=0.002 (highly significant)

Table 4. Visual menstrual bleeding scores (MS) and ferritin levels (ng/l) before and during treatment (observation period 12 months) in 12 FibroPlant® users with menorrhagia (score >185).

Study 5: FibroPlant® LNG-IUS in women with idiopathic menorrhagia assessed by the visual menstrual score technique: All women reported greatly reduced bleeding (Table 5). 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 to 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.

***A. Before treatment***

| | **No prior IUD use** | **Prior IUD use** |
|---|---|---|
| n | 17 | 15 |
| Mean | 337.9 | 368.0 |
| St. Dev. | 139.2 | 172.0 |
| Median | 324.2 | 328.8 |
| Minimum | 185 | 185 |
| Maximum | 740 | 890 |

Mann-Whitney U-test: p=0.63 (NS)

***B. During treatment***

| | **No prior IUD use** | **Prior IUD use** |
|---|---|---|
| n | 17 | 15 |
| Mean | 70.0 | 52.3 |
| St. Dev. | 52.8 | 51.3 |
| Median | 62.5 | 41.3 |
| Minimum | 5 | 3 |
| Maximum | 210 | 150 |

Mann-Whitney U-test: p=0.31 (NS)

Table 5. Analysis of the Visual Bleeding Scores comparison between the group with prior IUD use (n = 15) and the group with no prior IUD use (n = 17). A. Before treatment. B: During treatment

Study 6: Femilis® LNG-IUS in women with menorrhagia associated with intrauterine fibroids assessed by the visual menstrual score technique: All women reported greatly reduced bleeding, except one. In two women, the treatment failed although both reported reduced bleeding. One failure was due to the presence of a large endometrial polyp. This patient underwent hysterectomy. The other women had submucosal fibroids. She refused hysterectomy and is continuing treatment. In the other 12 patients, reduction of bleeding was apparent 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 treatment which is highly statistically significant ($p<0.001$) (Table 6). In 8 women, the bleeding reduced to very low scores.

| | Age | VBS before treatment | VBS during treatment |
|---|---|---|---|
| Mean | 45 | 455 | 100 |
| Std Deviation | 3 | 210 | 85 |
| Median | 45 | 410 | 71 |
| Range | 39 - 49 | 185 - 960 | 5 – 300 |

Table 6. Descriptive statistics: age and visual bleeding scores (VBS) before and during treatment

## 4. Discussion and conclusion

The intrauterine release of LNG alters the function of the endometrium. This phenomenon offers special benefits for users and a manner of local intrauterine therapy.

The reduction of menstrual blood loss is based on the antiproliferative action of the LNG-IUS on the endometrium. The morphology of the endometrium is considerably altered, showing massive decidualization of the stroma, atrophic glands, and sometimes atrophy of the whole functional layer.[20] Normal endometrium during the menstrual cycle produces many highly active compounds (e.g., prostaglandins, estrogen, and estro-progestogen-induced growth factors and other bioactive peptides). In the endometrium suppressed by LNG, the production of these compounds is down regulated. On the other hand, progestogen stimulates the synthesis of other factors such as prolactine receptor, cyclooxygenase-2, and insulin-like growth factor-binding protein-1.[21,22] Furthermore, a significant increase in uterine artery resistance occurs in LNG-IUS users 1 year after insertion which might contribute in reducing menstrual blood flow with the LNG-IUS.[23]

### 4.1 Treatment of idiopathic menorrhagia

The Mirena® LNG-IUS, releasing 20 µg of LNG/day has been compared with other medication in the treatment of menorrhagia.[24,25,26] Overall, the Mirena® LNG-IUS has been found to be more effective than conventional medication and treatment is also more economic. It was also found that the LNG-IUS was much more effective in reducing the mean MBL below the upper limit of normal MBL (<80 ml). When compared with transcervical endometrial resection (TCRE), both methods are equally effective. However,

endometrial destruction is not always complete. It could, therefore be beneficial to use the hormonal IUS in combination with endometrial destruction. The LNG-IUS, inserted just after the procedure, can be used to improve the results of endometrial resection. Maia et al.[27] reported the results of an interesting study. They investigated 106 women with HMB. After endometrial resection, the women were randomized into two groups, 53 women in each. Women in the treatment group were fitted with Mirena®. In this group, amenorrhoea was achieved in 72% of cases after 3 months, in 89% after 6 months and in 100% after 1 year. In the resection-only group, the corresponding numbers were 19%, 17% and 9%, and in this group, 19% of the women underwent a second resection.

Endometrial resection requires a specialist with endoscopic skills, and to be safe, well-equipped operation facilities. Endometrial ablation is associated with a higher risk of perioperative and long-term complications than use of a LNG-IUS. The cost over 5 years is high because of recurrences and hysterectomies. These are not problems in connection with the LNG-IUS. However, the most important difference between operative therapy and use of the LNG-IUS is that fertility is lost after the former treatment. On the other hand, women at risk for pregnancy and undergoing endometrial ablation should use effective contraception or consider being surgically sterilized, whereas the LNG-IUS provides effective contraception, and treats heavy menstrual bleeding.

In comparison with hysterectomy, morbidity (readmission for serious adverse events) is much higher in women undergoing surgery. In a recently conducted nationwide study in the UK, it was found that hysterectomy for benign indications, irrespective of surgical technique, increases the risk for subsequent stress-urinary-incontinence surgery.[28] In addition, the overall costs of surgery are about three times higher in women undergoing hysterectomy than in women using the Mirena® LNG-IUS.[29]

A recent Cochrane review on surgical versus medical therapy for heavy menstrual bleeding concluded that the Mirena® LNG-IUS provides a better alternative to surgery than oral medication.[30] Although hysterectomy is a definite treatment for heavy menstrual bleeding, it does not improve the overall quality of life significantly more than the LNG-IUS and can cause serious complications. Questions remains, however, about the long term clinical effectiveness of all the treatments; evidence from trials with longer term follow-up (four years or more) is limited. The LNG-IUS, in particular, versus alternative forms of surgical treatment requires further research.

The MBL studies reviewed in this report conducted with the T-shaped (Mirena®-like) LNG IUS, Femilis®, releasing 20 µg of LNG/day, and with the "frameless" FibroPlant® LNG- IUS, releasing 14 µg of LNG/day, in women with a normal menstrual pattern and in women with idiopathic menorrhagia, found a similar drastic reduction in MBL as in the studies conducted with the Mirena® LNG-IUS. Some of these studies are conducted over more than 5 years without recurrence of episodes of heavy periods.

### 4.2 Abnormal uterine bleeding in women certain subgroups of women

#### 4.2.1 Abnormal uterine bleeding in women with hemostatic disorders or using anticoagulant therapy

The most common underlying bleeding disorder is von Willebrand's disease, which occurs in only 1% to 2% of the general population but in approximately 13% of women with excessive menstrual bleeding. The diagnosis of von Willebrand's disease in healthy females with excessive menses is a true challenge to the gynaecological community. In such women,

bleeding disorders might be "mild," with menorrhagia being the only apparent clinical impact of the disorder. The diagnosis of von Willebrand's disease and other bleeding disorders might have an important impact on a woman and her family. It should be emphasized that gynaecologists should consider causes of excessive menstruation that are "outside the uterus" and that some pathology, such as subserosal or intramural leiomyomas, might indeed be asymptomatic. For women who are diagnosed with von Willebrand's disease and heavy menstrual bleeding, there is likely a benefit from the provision of the LNG-IUS.[31,32] Thus, the LNG-IUS appears to be an effective long-term treatment for HMB in women with inherited bleeding disorders (IBDs) in general. Also women having anticoagulant therapy could benefit from the LNG-IUS.[33,34]

#### 4.2.2 Excessive menstrual bleeding in adolescents

Menstrual disorders are common in adolescent girls in general. It commonly begins at menarche and can present acutely. This is usually secondary to anovulatory cycles caused by the immaturity of the hypothalamic-pituitary-ovarian axis. The condition adversely affects the QOL of affected adolescents. It can cause significant distress and discomfort in adolescent girls. It also has major health implications, such as iron deficiency anaemia and the need for hospitalization and blood transfusion in severe cases. It can affect their school attendance and performance. Treatment options include tranexamic acid, the combined oral contraceptive pill, the LNG-IUS, and specific hemostatic therapies, such as desmopressin and clotting factor replacement, if associated with inherent bleeding disorders.[35] These conservative treatment options should seek to avoid surgical intervention. When the LNG-IUS is selected, care should be taken to insert a device that fits in the usually small uterine cavity of these young women to maximize acceptance and continuation of use.

### 4.3 Heavy bleeding in intrauterine device users

Copper-releasing intrauterine devices may induce longer, heavier, and more painful periods. Pain and heavy menstrual bleeding are common reasons for discontinuing use of an intrauterine device within the first year. A recent Cochrane review evaluated data from 15 randomised controlled trials investigating the effect of NSAIDs on treatment or prevention of pain and bleeding due to an intrauterine contraceptive device.[36] Data from prevention trials were inconsistent. In otherwise asymptomatic women NSAIDs reduced pain or bleeding (or both) in three studies, did not differ from placebo in two studies, and reduced bleeding but not pain in another. A large trial of 2019 first time users in Chile did not support the prophylactic use of ibuprofen compared with placebo to reduce rates of removal of devices because of pain or bleeding.[37] Pain and/or abnormal, erratic or heavy menstrual bleeding is often caused by disharmony between the IUD and the uterine cavity (Figure 6). Recent 3-D sonography studies compared women with abnormally and those with normally located IUDs with respect to their indication for sonography and found that the proportion of patients whose principal indication for sonography was bleeding, pain or bleeding and pain were significantly greater in those with an abnormally located IUD, including imbedded IUDs, compared with those whose IUD was not located abnormally on 3-D sonography.[38,39] Clinical trials demonstrated, for the first time, the absence of a significant effect of the tiny GyneFix® IUD on menstrual blood loss due to its very small size and optimal harmony with the uterine cavity, leaving the cavity totally undisturbed.[40] This is important since abnormal bleeding and pain are the two major reasons for IUD

discontinuation.[41] In a Swedish study in CuT380A IUD users an increase in MBL was shown which ranged between 50 and 60%.[42]

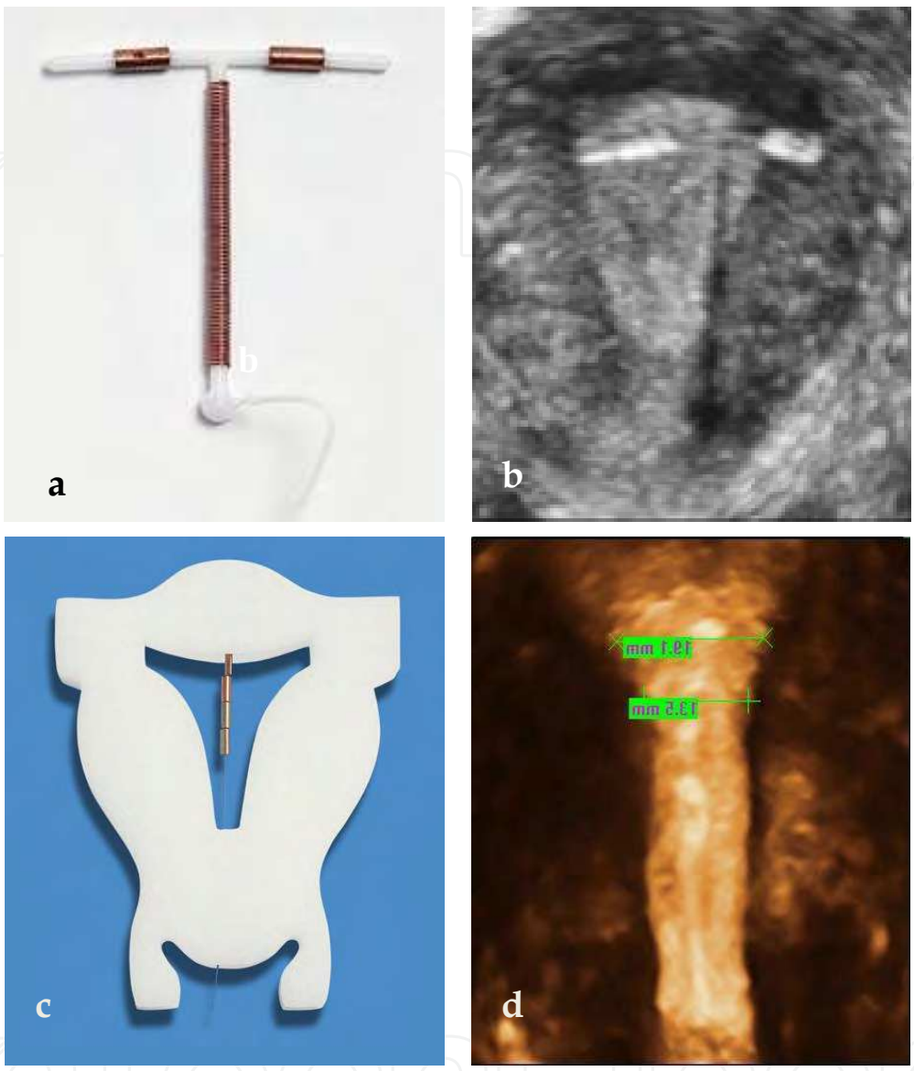



Fig. 6. a) Paragard® IUD; b) 3-D sonography of Paragard® in small uterine cavity of which the left arm penetrates the uterine wall (courtesy of Dr. B. Benacerraf); frameless GyneFix® IUD in foam uterus; 3-D sonographic picture of GyneFix® in narrow uterine cavity (courtesy of Dr. S. Jandi).

Many women can tolerate alterations in bleeding with copper-releasing IUDs. However, if the menstrual bleeding disturbances are causing discomfort or are too heavy, removal of the IUD will be requested. Of great importance are the long-term implications of excessive menstrual blood loss on iron stores with progressive development of iron depletion in IUD users, especially in developing country regions where the recipients of this contraceptive method are commonly of high parity and poor nutritional status. Kivijarvi et al. found clinical anaemia in 10% of users of copper IUDs after 12 months exposure and iron deficiency, as judged by the ferritin levels, could be demonstrated in 20%.[43] The effect of

MBL on iron stores was studied in Sweden which showed that the prevalence of iron deficiency anaemia doubled when MBL was between 60 and 80 ml and tripled when MBL was greater than 80 ml.[43,44] A significant drop in haemoglobin levels already occurs in women with an average menstrual blood loss of 66 ml over 12 menstrual cycles of IUD use.[45] The vulnerability of women in certain less developing parts of the world is indicated by the presence of iron deficiency in as many as 50% of women using an IUD, if a dietary supplement is not provided. It is probable that about 10% of women using an IUD risk secondary anaemia, especially those who bleed more than 80 ml per period. It has been suggested that an increased risk of iron deficiency exists even with a 40 ml blood loss.[46]
The main challenge of intrauterine contraceptive developers is to minimize menstrual side effects of IUDs without affecting efficacy and to reduce menstrual blood loss to enhance the health benefits of the method. Especially for women with low body iron stores, there is an order of preference for IUD use to minimize menstrual blood loss. The choice should first be a progestogen-releasing IUS, then a copper IUD which has the least effect on menstrual bleeding.

### 4.4 Treatment of menorrhagia associated with uterine fibroids

Although the main therapeutic approach in women with uterine leiomyomata remains surgery, 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.[47] GnRH agonists 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.[48]
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 anti-oestrogen on the breast, tamoxifen has an opposite effect on the endometrium as it acts as a partial estrogen agonist, rather than as an antagonist.[49]
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 success rate is less consistent especially in the presence of submucosal fibroids. The reduction in MBL in women with uterine fibroids was also confirmed in two recently published studies using the Mirena® LNG-IUS.[50,51] The results are similar with those reported by Wildemeersch et al.[12] Haemoglobin and ferritin levels increased significantly over 1 year of use. It appears that in women with a normal uterine cavity, a success rate in terms of a significant reduction in MBL close to 100% can be guaranteed.
The study conducted in women with significant fibroids (Study 6) confirms the 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. 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. The LNG-IUS significantly reduces uterine volume in women with menorrhagia with and without leiomyoma. The absence of significant reduction in the volume of leiomyomas was confirmed by others.[52] Decrease in size of leiomyomas is usually seen in menopausal women. In a study conducted by Inki and colleagues, no marked change was noted in the mean size of the fibroids. Further evaluation revealed that some had grown and some had shrunk.[53] Maruo and colleagues suggested that progesterone may have dual actions on uterine leiomyoma growth. By up regulating some endometrial proteins and down regulating tumor necrosis factor α, progesterone can stimulate leiomyoma growth, and by down regulating insulin-like growth factor-1 expression, inhibit growth.[54] Local autocrine or paracrine growth factor balance around each fibroid may define the direction of the effect.

Local delivery of other drugs such as mifepristone or another progesterone receptor modulator (PRM), with strong antiprogestogen activity and antiestrogenic effect at the endometrial level, may be more suitable to reduce the size of the fibroid tumors.

An additional advantage of the LNG-IUS is the highly appeasing effect of the treatment in women with dysmenorrhoea. Wildemeersch and colleagues showed a highly beneficial effect in women with dysmenorrhoea, confirming other studies, conducted with the frameless LNG-IUS in women with primary and secondary dysmenorrhoea.[55]

### 4.5 Treatment of anaemia due to heavy menstrual bleeding

Excessive MBL (>80 ml) is the most common cause of iron deficiency anaemia in women.[56] Many women, especially in developing countries, start their reproductive years with inadequate iron stores. Because of the closely spaced pregnancies, they have little time to build up their haemoglobin levels.[4] Each pregnancy makes them more vulnerable to serious ill health and death. A survey conducted by the World Health Organization reported a 19% prevalence rate of menorrhagia in 14 developing countries.[57]

An immediate and cost-effective solution is to provide women with a progestogen-releasing device to minimize MBL, especially for women with low body iron stores which will result in improved haemoglobin and ferritin levels. The use of the LNG-IUS is, therefore, an economical and logical approach when compared with alternatives such as hysterectomy or endometrial ablation.[6,25,58] The simultaneous provision of a long-acting and effective contraceptive may also be of substantial benefit to women.

## 5. Conclusion

We conclude with NICE (National Institute Clinical Excellence)[59]:

**Drug treatment**

"If history and investigations indicate that pharmaceutical treatment is appropriate and either hormonal or nonhormonal treatments are acceptable, treatments should be considered in the following order:

- Levonorgestrel-releasing intrauterine system, provided long-term (at least 12 months) use is anticipated.
- Tranexamic acid or non-steroidal anti-inflammatory drugs (NSAIDs) or combined oral contraceptives (COCs).

- Norethisterone (15 mg) daily from days 5 to 26 of the menstrual cycle, or injected long-acting progestogens."

"If hormonal treatments are not acceptable to the woman, then either tranexamic acid or NSAIDs can be used."

**Surgery**

"In women with heavy menstrual bleeding alone, with uterus no bigger than a 10-week pregnancy, endometrial ablation should be considered preferable to hysterectomy." The report makes clear that hysterectomy should only be considered as a last option. Commenting at its launch, Mary Ann Lumsden, a consultant in gynecology and chairwoman of the NICE guidelines development group that produced the report, said: "In the early 1990s it was estimated that at least 60 percent of women presenting with heavy menstrual bleeding would have a hysterectomy to treat the problem, often as a first-line treatment and without discussion of any alternative options. This should now be rare as it is fundamental that all women with heavy periods know there is a range of treatment options, many of which don't require surgery."

An additional advantage of the LNG-IUS is that it may also be beneficial in women with endometriosis, adenomyosis, fibroids and endometrial hyperplasia, conditions which are frequently associated with menorrhagia.[60,61,62]

Most patients are likely to select a non-invasive treatment. Avoiding major surgery, combined with no hospitalization and quick recovery, are seen as major advantages of non-invasive management. In women treated with the LNG-IUS, this device would be preferred over hysterectomy by 95% of the patients if the expected success rate were >50%.[63]

Endometrial destruction is the second-line treatment for menorrhagia but it can be considered as the first-line treatment for patients in whom other forms of treatment are unsuitable or if the risks relating to surgery are high. The insertion of an LNG-IUS following endometrial resection, to increase the rate of amenorrhoea, may be interesting in some cases.[27] The rationale is that up to 30% of patients need a subsequent procedure which can be avoided by the insertion of an LNG-IUS.

Being an effective contraceptive, together with the strong reduction of MBL, makes it a very attractive method for many women in developed and developing countries. The simple and safe insertion procedure of the Femilis® LNG-IUS could be an added advantage for use by non-specialist providers such as nurses, midwives and general practitioners who are practicing in remote areas as many women lack access to specialized treatment in these areas.

## 6. Acknowledgment

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

**Conflict of Interest:** Dirk Wildemeersch, MD, PhD, is a Belgian gynaecologist and Medical Director of Contrel Drug Delivery Research, an organization 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®, FibroPlant® and Femilis®. The research organization also provides insertion training for doctors. The funds generated are used for conducting further research and to participate in humanitarian projects.

## 7. References

[1] Edlund M, Magnuson C, von Schoultz B. Quality of life - a Swedish survey of 2200 women. In: Smith SK, ed. Dysfunctional uterine bleeding. London: Royal Society of Medicine Press, 1994.

[2] Coulter A, Bradlow J, Agass M. Outcomes of referrals to gynaecology outpatient clinics for menstrual problems: an audit of general practice records. Br J Obstet Gynaecol 1991;98;789-796.

[3] Clarke A, Black N. Rowe P, Mott S. Howie K. Indications for and outcomes of total abdominal hysterectomy for benign disease: a prospective cohort study. Br J Obstet Gynaecol 1995;102:611-620.

[4] Cameron IT and Smith SK. Menorrhagia. In: Haemostasis and thrombosis in obstetrics and gynecology. Ed. I Greer, A Turpie and C Forbes. Associated Books, London, 1992, pp. 77-93.

[5] Janssen CA, Scholten PC, Heintz APM. A Simple Visual Assessment Technique to Discriminate Between Menorrhagia and Normal Menstrual Blood Loss. Obstet Gynecol 1995;85,(6):977-982.

[6] World Health Organization. More than half of all pregnant women suffer from anaemia. WHO Presss Release WHO/17, 5 March 1993.

[7] Hurskainen R. Managing drug-resistant essential menorrhagia without hysterectomy. Best Practice &Research Clinical Obstetrics and Gynaecology Vol. 20, No. 5, pp. 681-694, 2006.

[8] Hurskainen R, Teperi J, Rissanen P et al. Clinical outcomes and costs with the levonorgestrel releasing intrauterine system or hysterectomy for treatment of menorrhagia: Randomized trial 5-year follow-up. JAMA: The Journal of the American medical Association 2004; 291: 1456-1463.

[9] Lethaby A, Cooke I, Rees M & Lethaby A. Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding. Cochrane Database of Systematic Reviews 2005; 4: CD002126.

[10] Reid PC & Virtanen-Kari S. Randomised comparative trial of the levonorgestrel intrauterine system and mefenamic acid for the treatment of idiopathic menorrhagia: a multiple analysis using total menstrual fluid loss, menstrual blood loss and pictorial blood loss assessment charts. British Journal of Obstetrics and Gynaecology 2005; 112: 1121-1125.

[11] Wildemeersch D, Schacht E. Treatment of menorrhagia with a novel 'frameless' intrauterine levonorgestrel-releasing drug delivery system, a pilot study. European Journal of Contraception and Reproductive Health Care 2001; 6, 93–101.

[12] Wildemeersch D, Schacht E The effect on menstrual blood loss in women with uterine fibroids of a novel 'frameless' intrauterine levonorgestrel-releasing drug delivery system, a pilot study. European Journal of Obstetrics, Gynecology and Reproductive Biology 2002;102:74-79.

[13] Andrade ATL, Souza JP, Andrade GN, Rowe PJ. Assessment of menstrual blood loss in Brazilian users of the frameless copper-releasing IUD with copper surface are of 330 mm² and the frameless levonorgestrel-releasing intrauterine system. Contraception 2004;70:173-7.
[14] Wildemeersch D, Rowe PJ. Assessment of menstrual blood loss in women with idiopathic menorrhagia using the frameless levonorgestrel-releasing intrauterine system. Contraception 2004;70:165-168.
[15] Wildemeersch D, Rowe PJ. Assessment of menstrual blood loss in Belgian users of a new T-shaped levonorgestrel-releasing intrauterine system. Contraception 2005;71:470-473.
[16] Hallberg L, Nilsson L. Determination of menstrual blood loss. Scandinav J Clin Lab Invest 1964;16:244-48.
[17] Shaw ST Jr. On quantifying menstrual blood loss. Contraception 1977;16:283-285.
[18] Newton J, Barnard G, Collins W. A rapid method for measuring menstrual blood loss using automatic extraction. Contraception 1977;16:269-82.
[19] Andrade ATL, Souza JP, Shaw ST Jr, Belsey EM, Rowe PJ. Menstrual blood loss and body iron stores in Brazilian women. Contraception 1991;43:241-49.
[20] Silverberg SG, Haukkamaa M, Arko H, Nilsson CG, Luukkainen T. Endometrial morphology during long-term use of levonorgestrel-releasing intrauterine devices. Int J Gynecol Pathol 1986;5:235-241.
[21] Jones RL, Critchly HO. Morphological and functional changes in the endometrium following intrauterine levonorgestrel delivery. Hum Reprod 2000;15 (suppl 3):162-72.
[22] Rutanen E-M. Insulin-like growth factors and insulin-like growth factors binding proteins in the endometrium: effect of intrauterine levonorgestrel delivery. Hum Reprod 2000;15 (suppl 3):173-81.
[23] Haliloglu B, Celik A, Ilter E, Bozkurt S, Ozekici U Comparison of uterine artery blood flow with levonorgestrel intrauterine system and copper intrauterine device. Contraception 83 (2011) 578-81.
[24] Nath Roy S, Bhattacharya S. Benefits and risks of pharmacological agents used for the treatment of menorrhagia. Drug Safety 2004;27:75-90.
[25] Milson I, Andersson K, Andresch B, Rybo G. A comparison of flurbiprofen, tranexamic acid and a levonorgestrel intrauterine contraceptive device in the treatment of idiopathic menorrhagia. Am J Obstet Gynecol 1991;164:879-83.
[26] Kaunitz AM, Meredith S, Inki P, Kubba A, Sanchez-Ramos L. Levonorgestrel-Releasing Intrauterine System and Endometrial Ablation in Heavy Menstrual Bleeding. A Systematic Review and Meta-Analysis. Obstet Gynecol 2009; 113: 1103-16.
[27] Maia H Jr, Maltez A, Coelho G, Athayde C, Coutinho EM. Insertion of mirena after endometrial resection in patients with adenomyosis. J Am Assoc Gynecol Laparosc. 2003; 10:512-6.
[28] Altman D, Granath F, Cnattingius S, Falconer C. Hysterectomy and risk of stress-uriniary-incontinence. The Lancet 2007; 370:1494-1499. BMJ 2010;341: c3929doi: 10.1136/bmj.c3929.
[29] Hurskainen R, Teperi J, Rissanen P, Aalto AM, Grenman S, Kivelä A, Kujansuu E, Vuorma S, Yliskoski M, Paavonen J. Clinical outcomes and costs with the levonorgestrel-releasing intrauterine system or hysterectomy for treatment of menorrhagia. JAMA 2004;291:1456-63.

[30] Majorbanks J, Lethaby A, Farquhar C. Surgery versus medical therapy for heavy menstrual bleeding. Cochrane Database System Review 2003;(2):CD003855.
[31] Lukes AS, Kadir RA, Peyvandi F, Kouides PA. Disorders of hemostasis and excessive menstrual bleeding: prevalence and clinical impact. Fertil Steril 2005;84:1338-44.
[32] Munro MG, Lukes AS for the Abnormal Uterine Bleeding and Underlying Hemostatic Disorders Consensus Group: Abnormal uterine bleeding and underlying hemostatic disorders: report of a consensus process. Fertil Steril 2005;84:1335-7.
[33] Chi C, Huq FY, Kadir RA. Levonorgestrel-releasing intrauterine system for the management of heavy menstrual bleeding in women with inherited bleeding disorders: long-term follow-up. Contraception 83 (2011) 242-7.
[34] Kadir RA, Chi C. Levonorgestrel intrauterine system: bleeding disorders and anticoagulant therapy. Contraception 75 (2007) S123-S129.
[35] Chi C, Pollard D, Tuddenham EGD, Kadir RA. Menorrhagia in Adolescents with Inherited Bleeding Disorders. J Pediatr Adolesc Gynecol 2010;23:215-22.
[36] Grimes DA, Hubacher D, Lopez LM, Schulz KF. Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use. Cochrane Database Syst Rev 2006;(4):CD006034.
[37] Hubacher D. Preventing copper IUD removals due to side effects among first time users: placebo-controlled randomized controlled trial to study the effect of prophylactic ibuprofen. Hum Reprod 2007;21:1467-72.
[38] Benacerraf BR, Shipp TD, Bromly B. Three-dimensional ultrasound detection of abnormally located intrauterine contraceptive devices which are the source of pelvic pain and abnormal bleeding. Ultrasound Obstet Gynecol 2009; 34: 110-5.
[39] Shipp TD, Bromly B. Benacerraf BR. The width of the uterine cavity is narrower in patients with an embedded intrauterine device (IUD) compared to a normally positioned IUD. J Ultrasound Med 2010; 29: 1453-6.
[40] Wildemeersch D, Rowe PJ. Assessment of menstrual blood loss in Belgian users of the frameless copper-releasing IUD with copper surface area of 200 mm2 and users of a copperlevonorgestrel-releasing intrauterine system. Contraception 2004;70: 169-72.
[41] Wildemeersch D, Rowe PJ. Assessment of menstrual blood loss in women with idiopathic menorrhagia using the frameless levonorgestrel-releasing intrauterine system. Contraception 2004; 70: 165-8.
[42] Milsom I, Andersson K, Jonasson K, Lindstedt G, Rybo G. The influence of the Gyne-T 380s IUD on menstrual blood Loss and iron status. Contraception 1995; 52: 175-9.
[43] Kivijarvi A, Timoneb H, Rajamaki A, Gronroos M. Iron deficiency in women using copper intrauterine devices. Obstet Gynecol 1986; 67: 95-8.
[44] Hallberg L, Högdahl AH, Nilsson L, Rybo G. Menstrual blood loss, a population study. Acta Obstet Gynec Scand 1966;45:320-51.
[45] Guillebaud J, Bonnar J, Morehead J, Mathews A. Menstrual blood loss with intrauterine devices. Lancet 1976;21:387-90.
[46] Jacobs A, Butler EB. MBL in iron deficiency anemia. The Lancet 1965;11:407-9.
[47] Nisolle M and Donnez J. Medical management of uterine fibroids: short-term therapy with GnRH agonists. In: Brosens I, Lunenfeld B, Donnez J, eds. Pathogenesis and medical management of uterine fibroids. Carnforth, UK: Parthenon Publishing, 1999:113-119.

[48] Donnez J, Gillerot S, Squifflet J and Nisolle M. Progestogens and antiprogestogens. In: Brosens I, Lunenfeld B, Donnez J, eds. Pathogenesis and medical management of uterine fibroids. Carnforth, UK: Parthenon Publishing, 1999:121-128.

[49] Assakis VJ, Jordan VC. Gynecological effects of tamoxifen and the association with breast carcinoma. Int J Gynecol Obstet.1995, 49:241-257.

[50] Grigorieva V. Chen-Mok M, Tarasova M, et al. Use of a levonorgestrel-releasing intrauterine system to treat bleeding related to uterine leiomyomas. Fert Steril 2003;79:1194-8.

[51] Mercorio F, De Simone R, Di Spiezio Sardo A, et al. The effect of a levonorgestrel-releasing intrauterine device in the treatment of myoma-related menorrhagia. Contraception 2003;67:277-80.

[52] MagalhÃ£es J, Aldrighi JM, de Lima GR: Uterine volume and menstrual patterns in users of the levonorgestrel-releasing intrauterine system with idiopathic menorrhagia or menorrhagia due to leiomyomas. Contraception; 2007;75:193-8.

[53] Inki P, Hurskainen R. Palo P, et al. Comparison of ovarian cyst formation in women using the levonorgestrel-releasing intrauterine system vs. hysterectomy. Ultrasound Obstet Gynecol 2002;20:381-85.

[54] Maruo T, Matsuo H, Shimomura Y. et al. Effects of progesterone on growth factor expression in human uterine leiomyoma. Steroids 3003;68:817-24.

[55] Wildemeersch D, Schacht E, Wildemeersch P. Treatment of primary and secondary dysmenorrrhoea with a novel "frameless" intrauterine levonorgestrel-releasing drug delivery system: a pilot study. Eur J Contracept & Reprod Health Care 2001;6:192-198.

[56] Cohen BJ, Gibor Y. Anemia and menstrual blood loss. Obstet Gynecol Surv 1980;35:597-618.

[57] Wood C. Menorrhagia: a management update. Modern Medicine of Australia 1999;42:65-75.

[58] Hurskainen R. Managing drug-resistant essential menorrhagia without hysterectomy. Best Practice &Research Clinical Obstetrics and Gynaecology Vol. 20, No. 5, pp. 681-694, 2006.

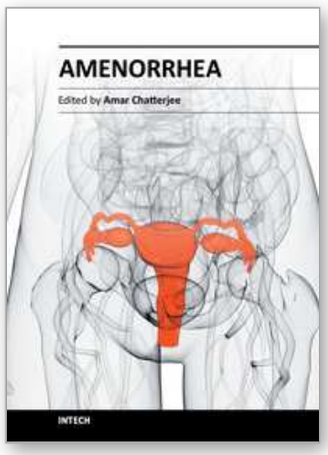
[59] National Institute Clinical Excellence (NICE, UK).[59] New guidelines on heavy menstrual bleeding. Issue 05: 5 mar 2007 (www.nice.org.uk/cg044).

[60] Bahamondes L, Petta CA, Fernandes A, Monteiro I. Use of the levonorgestrel-releasing intrauterine system in women with endometriosis, chronic pelvic pain and dysmenorrheal. Contraception 75 (2007) S134–S139.

[61] Fedele L, Bianci S, Raffaelli R, Portuese A, Dorta M. Treatment of adenomyosis-associated menorrhagia with a levonorgestrel-releasing intrauterine device. Fertil Steril. 1997 Sep;68(3):426-429.

[62] Wildemeersch D, Pylyser K, De Wever N, Dhont M. Treatment of non atypical and atypical endometrial hyperplasia with a levonorgestrel-releasing intrauterine system: long-term follow-up. Maturitas 57 (2007) 210–213.

[63] Boudrez P, Bongers MY, Mol BWJ. Treatment of dysfunctional uterine bleeding: patient preferences for endometrial ablation, a levonorgestrel-releasing intrauterine device, or hysterectomy. Fert Steril 2004;82:160-166.




**Amenorrhea**

Edited by Prof. Amar Chatterjee

ISBN 978-953-307-988-2

Hard cover, 148 pages

**Publisher** InTech

**Published online** 09, December, 2011

**Published in print edition** December, 2011

This book on "Amenorrhea" is a wonderful collection of updated reviews dealing mostly with the aphysiological aspects of secondary amenorrhea. The book represents a collection of eight chapters, each chapter in the book is written by the international experts with extensive experience in the areas covered. We hope that readers will find this book interesting, helpful and inspiring.

**How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

D. Wildemeersch and A. Andrade (2011). From Heavy Menstrual Bleeding to Amenorrhoea and Reversal of Anaemia - Novel, Effective, Intrauterine Levonorgestrel-Releasing Systems for Contraception and Treatment, Amenorrhea, Prof. Amar Chatterjee (Ed.), ISBN: 978-953-307-988-2, InTech, Available from: http://www.intechopen.com/books/amenorrhea/from-heavy-menstrual-bleeding-to-amenorrhoea-and-reversal-of-anaemia-novel-effective-intrauterine-le

INTECH
open science | open minds

**InTech Europe**
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

**InTech China**
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen