

Femilis® 60 Levonorgestrel-Releasing Intrauterine System—A Review of 10 Years of Clinical Experience



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ABSTRACT

OBJECTIVE: The aim of this study was to update the clinical experience with the Femilis® 60 levonorgestrel-releasing intrauterine system (LNG-IUS), now up to 10 years in parous and nulliparous women, particularly with regard to ease and safety of insertion, contraceptive performance, retention, acceptability, continuation of use, impact on menstrual blood loss (MBL), and duration of action.

STUDY DESIGN: Using the Femilis® 60 LNG-IUS releasing 20 µg of levonorgestrel/day, the following studies were conducted: an open, prospective noncomparative contraceptive study, an MBL study, a perimenopausal study, a study for the treatment of endometrial hyperplasia, and early cancer of the uterus, a residue study.

RESULTS: A total of 599 Femilis LNG-IUS were inserted in various clinical trials, the majority for contraceptive purposes. The total exposure in the first and second contraceptive studies, covering 558 parous and nulliparous women, was 32,717 woman-months. Femilis has high contraceptive effectiveness as only one pregnancy occurred. Expulsion of the LNG-IUS was rare with only two total and no partial expulsions (stem protruding through the cervical canal) occurred. Femilis was well tolerated, with continuation rates remaining high. Several MBL studies were conducted, totaling 80 heavy and normal menstrual bleeders, using the pictorial bleeding assessment chart method or the quantitative alkaline hematin technique. Virtually all women responded well with strongly reduced menstrual bleeding. Amenorrhea rates were high, up to 80% after three months, and ferritin levels simultaneously increased significantly. The Femilis LNG-IUS was tested in 104 symptomatic perimenopausal women for seamless transition to and through menopause, adding estrogen therapy when required. Patient tolerability appeared high as >80% requested a second and a third LNG-IUS. Twenty women presenting with nonatypical and atypical hyperplasia and one woman presenting with early endometrial carcinoma were treated with Femilis LNG-IUS. All histology specimens showed full regression, and patients remained in remission without signs of hyperplasia or cancer at yearly and ongoing follow-up examinations up to 10 years. Residual content of LNG was measured in 37 women having the Femilis LNG-IUS for up to 10 years. In 10 of the 102 women who had the Femilis 60 in situ for 10 years between 20% and 30% of the original 60 mg was recovered confirming the long duration of action of the Femilis 60 LNG-IUS.

CONCLUSION: These studies suggest that the Femilis 60 LNG-IUS releasing 20 µg of LNG/day is an effective, well-tolerated, and well-retained contraceptive both in parous and in nulliparous women. The design of the LNG-IUS, with flexible transverse arm(s) length of 28 mm, allows for a simplification of the insertion technique and training requirements facilitating the use by nonspecialist providers in either developed or developing countries. For nulliparous women, additional evaluation of devices with a 24 mm transverse arm(s), as it relates to tolerability, retention, and continuation of use, still needs to be undertaken.

KEYWORDS: T-shaped intrauterine system, levonorgestrel, contraception, heavy menstrual bleeding, hormone replacement therapy, hyperplasia, endometrial cancer

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Introduction

The Mirena® intrauterine system (Bayer Healthcare, Germany) was developed in Finland in the 1970s. Remarkably, the aim of the development was to reduce the risk of intrauterine device expulsion and not to enhance the contraceptive performance of intrauterine devices (IUDs).¹ The first report was published in 1975.² The contraceptive effectiveness of the levonorgestrel-releasing intrauterine system (LNG-IUS) was thoroughly studied in several large randomized comparative clinical trials compared to the TCu380A IUD (Paragard®;

Teva Pharmaceuticals, USA).^{3–5} These studies, lasting for periods of up to seven years, with the collective exposure of 12,000 woman-years, revealed a high cumulative effectiveness rate of 0.5%–0.7% over five years. The cumulative expulsion rates of 10.6% for Mirena at three years and between 5.8% and 11.8% at five years were observed in these trials. Patient continuation rates at five years were less than 50% for both IUDs. The majority of these trials were conducted exclusively in parous women. In subsequent studies, when used in nulliparous women, the Mirena first-year expulsion rates of up to



13.3% and the first-year removal rates for bleeding and pain of up to 21.5% were observed.^{6–9} Some authors commented that intrauterine contraceptives not fitting properly within the uterine cavity contributed to early discontinuation.¹⁰ Hubacher's review of copper IUDs revealed that nulliparous women experience higher rates of expulsion and removals for bleeding and/or pain compared with parous women.¹¹ The noncontraceptive beneficial effects of LNG-IUS were reviewed recently as a consequence of its pronounced progesterone-like properties.^{12–15} They are, however, still not fully appreciated by many health-care providers. The hormone released from the IUS causes significant local effect characterized by glandular atrophy and stromal decidualization. This dominant suppressive effect of the endometrium is seen through the whole thickness of the endometrium resulting in thickening of the arterial walls with capillary thrombosis.¹⁶ The end result is a suppression of menstrual bleeding as the endometrium becomes insensitive to estradiol. The effect of the LNG-IUS for the treatment of heavy menstrual bleeding (HMB) has been studied thoroughly and has also been compared with oral medication and endometrial resection and ablation techniques.^{17–22} These studies confirm the superior effectiveness of the LNG-IUS compared with oral hormone administration, and there appears to be little difference in the reduction of menstrual blood loss (MBL) compared with endometrial ablation. The success rate of endometrial ablation techniques may even be significantly enhanced, if a LNG-IUS is inserted following the procedure.^{23,24}

In view of it being the most effective nonsurgical method for the treatment of HMB, the LNG-IUS has also been studied in women with disorders of hemostasis, HMB in association with uterine fibromyoma and adenomyosis.^{25–27} Despite the observation that MBL decline is slower in women with fibroids, most women with HMB and fibroids gain a dramatic benefit from MBL reduction and may often escape hysterectomy.²⁸ As a consequence of HMB, many women develop severe iron-deficiency anemia, which can be reversed by suppressing the endometrium with LNG-IUS.²⁹ In addition, several clinical studies demonstrated the pronounced impact of the LNG-IUS on HMB in women with adenomyosis. Adenomyosis is a frequent cause of abnormal uterine bleeding and pain. A reduction in uterine volume was also observed in these women.^{30–33} Women can also benefit from a LNG-IUS impact on the endometrium in case of endometrial hyperplasia and in precancerous atypical hyperplasia and early cancer of the endometrium. Regression of nonatypical and atypical hyperplasia has been observed by several investigators. They reported a complete regression in women with benign hyperplasia without nuclear atypia and regression in more than two-thirds of women with atypia.³⁴ Recently, higher regression rates have been observed in women with complex atypical hyperplasia, but some failures were also observed.^{35,36} Women with pelvic endometriosis may expect a favorable response that starts early after insertion of

a LNG-IUS with a significant reduction in pain complaints as seen with GnRH analog treatment.^{37,38} Direct effect of the hormone on the endometrial lesions may explain the therapeutic effect as the concentration of LNG in the peritoneal fluid of LNG-IUS users is approximately two-thirds of those obtained in serum.³⁹ The potential contraceptive and noncontraceptive benefits of LNG-IUS are considerable and well-known by the medical profession. Long-acting contraceptive methods are starting to reduce the number of tubal sterilizations and hysterectomies for the treatment of benign conditions, such as HMB and nonatypical endometrial hyperplasia.^{40,41}

The LNG-IUS also has an important role in the disease prevention of uterine pathologies, such as endometrial polyps, endometrial cancer, and tamoxifen-induced changes, and even in the prevention of pelvic inflammatory disease.⁴² The LNG-IUS unfortunately also has some drawbacks that may have led to lawsuits against this contraceptive method.⁴³ Many of these cases are unsubstantiated by medical science. The availability of the LNG-IUS remains crucial for women as it has become the method of choice of many gynecologists to prevent unintended pregnancy and treat gynecological conditions which no other nonsurgical method can provide.

This paper reviews the clinical results of a new T-shaped LNG-IUS, potentially offering some advantages that may avoid some of the disadvantages of the existing LNG-IUSs.

Materials and Methods

Description of the Femilis® 60 LNG-IUS and insertion procedure. Femilis® (APCOR R&M, Belgium) consists of a 3 cm long and a 2.4 mm wide drug delivery compartment. The inert vector is made of ethylene vinyl acetate copolymer, containing 60 mg of LNG, and is covered by a rate-controlling membrane, equally made of ethylene vinyl acetate. The drug delivery compartment releases approximately 20 µg of LNG in vitro daily. The mean in vivo drug release rate during the first five-year period is approximately 14 µg/day. The drug compartment is provided with transverse retention arms with a total length of 28 mm long (devices with transverse arms of 24 mm have still to be tested), fixed to the upper part of the drug delivery rod. The polyethylene transverse arms contain 22% barium sulfate to render it radiopaque. The single tail is made of a 00 G polypropylene (Fig. 1). The Femilis LNG-IUS is inserted using the following push-in technique (Fig. 2): Step 1: The loaded inserter is applied against the cervix; Step 2: Femilis is pushed into the uterine cavity up to the fundus; and Step 3: The inserter tube is removed and the thread is trimmed. The proper positioning of the LNG-IUS in the uterine cavity is easily assessed by means of abdominal or vaginal ultrasound examination.

The insertion of Femilis is apparently simpler than that required for other conventional T-shaped devices, since its arms are folded downward during the insertion process. The transverse arms unfold immediately upon approaching the uterine fundus allowing for self-positioning of the device. In contrast, devices such as Mirena/Skylla are internal to the



Figure 1. Femilis® LNG-IUS with drug delivery rod functioning as the stem of the IUS and horizontal transverse arms.

inserter, and upon release, the arms protrude upward. The clinicians need to coordinate withdrawal of the inserter while simultaneously pushing the IUD forward, being cautious not to perforate the uterus but to assure proper placement.

Contraceptive study. The total number of women in the contraceptive study was 558. A total of 118 women in the nulliparous group received the smaller T-shaped Femilis Slim LNG-IUS (with a thin transverse arm(s) of 24 mm) and were omitted from the analysis given its differences from Femilis. Femilis Slim was developed for use in both nulliparous and postmenopausal women with a small uterine cavity. As it is a very thin and of flexible design it could not be retained in the uterus of all normal women and therefore resulted in a slightly greater number of expulsions relative to the larger Femilis itself. Femilis Slim was, however, found in clinical trials to be ideally suited for use in postmenopausal women for the alleviation of menopausal symptoms in conjunction with estrogen supplementation, since the uterus in these women is quiescent that aids in retention.

The details of the contraceptive study with Femilis 60 LNG-IUS have been published earlier.⁴⁴ All of the data that

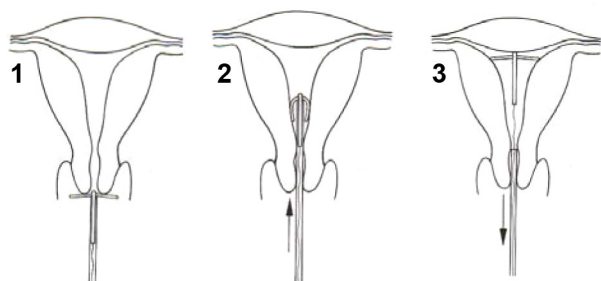


Figure 2. Simplified push-in insertion procedure of the Femilis LNG-IUS. Step 1: The loaded inserter is applied against the cervix. Step 2: Femilis is pushed into the uterine cavity up to the fundus. Step 3: The inserter tube is removed and the thread is trimmed. The proper positioning of the LNG-IUS in the uterine cavity is easily assessed by means of abdominal or vaginal ultrasound examination.

were generated during the study were transferred to the data-coordinating center at the Department of Medical Informatics and Statistics, University Hospital, Gent, Belgium. Besides effectiveness, the rates of discontinuation for individual reasons and groups of reasons were analyzed using the S-PLUS statistical software package (Mathsoft Corp),⁴⁵ and the cumulative discontinuation rates were computed using survival analysis methods.^{46,47}

MBL studies. In 60 Belgian women, using the Femilis 60 LNG-IUS for 4 to >30 months, MBL was assessed with the pictorial bleeding assessment chart technique described by Janssen et al.⁴⁸ Twenty-eight women had normal menstrual periods at baseline (menstrual score < 185), and 32 women had idiopathic menorrhagia (menstrual score > 185). The visual assessment technique does not yield an exact flow in milliliters, but, in practice, the sensitivity and specificity is reasonably high and superior to a woman's subjective assessment of MBL.

Twenty normal and heavy menstruating women (>80 mL) were included in a second MBL study conducted in Brazil. MBL was assessed by the quantitative alkaline hematin technique. MBL was quantified according to the technique first described by Hallberg and Nilsson⁴⁹ adapted by Shaw⁵⁰ and modified by Newton et al⁵¹ before insertion (baseline controls) of the LNG-IUS and after 3, 6, and 12 months. Women were instructed by a nurse to carefully collect their menstrual tampons and bring them to the laboratory in opaque plastic bags as soon as bleeding ended, as described previously.⁵² Serum ferritin was measured at the same intervals as described earlier. Women were followed up for 12 months.

Endometrial suppression in perimenopausal women using estrogen replacement therapy. Femilis 60 LNG-IUS was tested in 104 symptomatic perimenopausal women who requested estrogen replacement therapy, in combination with contraception, for the alleviation of their climacteric symptoms. Following expiry of the first Femilis LNG-IUS, a second LNG-IUS was inserted and subsequently a third LNG-IUS was made available to patients who wished to continue estrogen therapy. All women were treated with estradiol by the parenteral route of administration.

Endometrial suppression in women with endometrial hyperplasia and early endometrial cancer. Twenty women presenting with nonatypical and atypical hyperplasia and one woman presenting with early endometrial carcinoma were treated with the frameless Fibroplant® (APCOR R&M, Belgium) or the Femilis 60 LNG-IUS. Fibroplant is a frameless LNG-IUS and is retained in the uterus with a small anchor inserted in the fundus of the uterus (Fig. 3).

Although having different retention mechanisms, the LNG releasing fiber is identical between both systems capable of releasing LNG at a rate of 20 µg/day. The histopathological diagnosis (Kurman classification)⁵³ was nonatypical (simple) hyperplasia in 12 women and atypical hyperplasia in



Figure 3. Fibroplant® LNG-IUS is frameless and anchored in the fundus uteri with a nonbiodegradable surgical knot, which is pushed into the myometrium over a controlled depth using a specially designed inserter. Due to the absence of a frame, Fibroplant fits in the cavities of every size and shape.

8 women (adenomatous hyperplasia with atypia in 3 women among them). In one of the latter patients, an invasive well-differentiated adenocarcinoma was found on D&C, but this was not confirmed in two subsequent endometrial pipelle samplings. In one additional patient, an early, moderately differentiated adenocarcinoma of the endometrium was diagnosed.

Duration of action of the Femilis® 60 LNG-IUS.

High-performance liquid chromatography coupled with ultra violet detection, following preparation of the test solution for the determination of LNG content in used and fresh Femilis 60 LNG-IUS after LNG extraction conducted by the University of Liège (APCOR R&M, data on file) to calculate the in vivo release rate and duration of release, was performed. The physical changes of the drug delivery rod after 10 years in situ were evaluated by inspection and by measuring the diameter of the drug compartment with a precision instrument.

Results

Contraceptive study. The interim efficacy and safety results of the contraceptive study that started in 2002 were published previously.⁴⁴ The total number of women at the time of analysis in the main contraceptive study is 558 women. However, as 118 nulliparous women received the smaller type of LNG-IUS (Femilis Slim with transverse arm(s) length totaling 24 mm) in the beginning of the study, they were not included in the current analysis.

Of the 440 remaining women, 371 among them were suitable for analysis but, as 69 women were older than 48 years at the time of analysis and were too close to menopause or

already menopausal to contribute meaningful to a contraceptive study, these subjects were also dropped from the analysis. A further 15 women were removed from the analysis as no follow-up could be conducted in these women. Thus, a total number of 356 women were analyzed.⁵⁴ Of these 356 women, 67.1% of the insertions were in parous and 32.9% of the insertions were in nulliparous women with the mean age of 35.1 years (range 15–48 years). One hundred forty-eight women (41.6%) were less than 35 years at study entry. The total observation period was 27,269 woman-months. Only one pregnancy was observed in this study, and only two expulsions were reported at five years. There were 41 removals for medical reasons (11.5%), of which 17 removals were related to bleeding and pain complaints and 24 removals were categorized as *removal for other medical reasons*, related to or not related to the use of the Femilis LNG-IUS (eg, mood changes, weight gain, migraine, pigmentation, hair loss, labia minora swelling, operation for fibroids, vaginal discharge, and breast and cervical cancers). Of the 356 women, 10 women (2.8%) were lost to follow-up and could not be contacted by telephone or letter. Women with minor complaints usually continued to use the LNG-IUS as most complaints disappeared with time. There were 45 removals (12.6%) for desire to become pregnant. The continuation rate at five years amounts to 74.3%, which includes the women who requested removal of the LNG-IUD to become pregnant. If these are excluded from the analysis, the continuation rate at five years would increase to 87.1%. The Femilis 60 LNG-IUD was well accepted by the majority of parous and nulliparous women. There were neither perforations nor PID cases reported during or following insertion.

A separate analysis suggested that the push-in technique of insertion is considered simple and safe. Insertion was reported to be easy in virtually all women (97.9%). Pain at insertion was absent in 24.7% and mild in 67.7% of women.⁵⁵ There were no serious adverse events at insertion (eg, perforation).

MBL studies.

Pictorial bleeding assessment chart study. The mean age was 40.3 years (range 22–48 years), and the mean duration of use of the Femilis 60 LNG-IUS was 17.6 months (range 4–31 months). 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 5 (range 0–150) at the last follow-up, a decrease of 96%. In women with menorrhagic bleeding (score >185) at baseline, menstrual flow dropped from a median score of 232 (range 185–450) at baseline to a median score of 3 (range 0–50) at the last follow-up visit, a decrease of 99%. Twenty women developed amenorrhea (33%): 10 in the group of women with normal menstruation and 10 in those women with HMB. Most of the remaining women had strong oligomenorrhea requiring the use of panty-liners only. In one woman, MBL did not decrease for no apparent reason, thus



requiring further evaluation.⁵⁶ No serious adverse events were recorded in this study.

Quantitative MBL study. The quantitative MBL study was conducted in 20 Brazilian women seeking contraception with heavy bleeding ($n = 6$) with the mean MBL of 137.4 mL (range 83.7–191.2 mL) and in normally menstruating women ($n = 14$) with the mean MBL of 40.5 mL (range 21.5–59.4 mL). MBL was reduced from a mean baseline menstrual volume of 64.3 mL in all women to a mean volume of 3.4 mL after 12 months, while ferritin values increased from a mean value of 102.5 ng/mL (at baseline) to a mean level of 198.9 ng/mL (after 12 months of use). The mean MBL in all women was 4.2 mL after three months with 16 out of 20 being amenorrhic. Differences were highly significant ($P < 0.0005$). There were no significant differences in impact on MBL between those who had normal menstrual bleeding and the heavy bleeders. The heavy bleeders had comparable MBL as the normal bleeders three months after insertion and 12 months postinsertion. Their ferritin levels were comparable with those of the normal bleeders. Amenorrhea occurred in 80% of women after three months of use. At six months, all were amenorrhic, except two, one with normal and one with scant menstrual bleeding. No pregnancies and no serious adverse events were recorded.

Study in perimenopausal women using estrogen replacement therapy. The study was conducted in 104 perimenopausal users using estrogen supplements. The average age of the women receiving the first Femilis LNG-IUS was 48 years (range 28–58 years), and the average duration of use of the regimen (first and second LNG-IUS combined) was 137 months (range 80–161 months). One woman was still not menopausal at the age of 58 years. Of the 104 women in the study, all received a second LNG-IUS. Following expiry of the second LNG-IUS, 86 (82%) opted for the replacement of a third LNG-IUS and are continuing to use the combined estrogen therapy and LNG-IUS regimen. Seven women were lost to follow-up; in the other women, the LNG-IUS was removed for various reasons (eg, breast cancer (2), hysterectomy for fibromyoma (2), and other reasons including moving away from the area and removal by another doctor at expiry of the LNG-IUS).⁵⁷ Women were generally happy with the regimen. No serious device-related adverse events were recorded.

Study in patients with endometrial hyperplasia and early cancer of the uterus. The average age of patients at study entry was 54 years (range 41–67 years), and the average duration of use of the LNG-IUS was 32 months (range 14–90 months). All women developed a thin endometrium (≤ 4 mm in thickness), as assessed by transvaginal ultrasound, except one patient. The latter patient presented with a polypoid structure of 20 mm in diameter prior to treatment that diminished gradually in size to 5 mm at the last follow-up examination, 53 months after insertion of the LNG-IUS. At study initiation, all women presenting with atypical endometrial hyperplasia showed the expression of progesterone receptors in

the epithelial cells. The percentage declined significantly over time during treatment. The endometrial histology specimen showed no progression of disease. Profound endometrial suppression with glandular atrophy and/or stromal decidualization was found in all women. Eight of the 20 women who used estrogen before treatment resumed estrogen treatment after histology of the endometrium normalized. All women continued to use the method.⁵⁸

Duration of action of the Femilis® 60 LNG-IUS.

One hundred two women had the LNG-IUS in place during a 10-year period. Thirty-seven Femilis samples, 18 after five years, 9 after 7.5 years, and 10 after 10 years, were evaluated. After five years, the mean residual content of LNG was 59.78% (range 35.97%–86.29%); after 7.5 years, the mean recovery of LNG was 46.83% (range 34.76%–51.57%); and after 10 years, the mean content of LNG was 30.04% (range 11.04%–39.69%). The mean calculated in vivo release rates were 13.30 ± 3.27 $\mu\text{g/day}$ during the first 5 years, 12.96 ± 3.19 $\mu\text{g/day}$ during the 7.5 years, and 12.50 ± 3.08 during the 10-year period. The only significant change of the device evaluated in 12 women after 10 years in situ was a reduction in the diameter of the drug delivery rod from ~ 2.4 to ~ 2.2 mm (range 2.15–2.28 mm) consistent with the release of LNG overtime (APCOR R&M, data on file).

Discussion

Many of us still remember the time as young physicians when only plain plastic IUDs existed, followed by the introduction of slimmer copper-bearing IUDs and later by the progesterone-releasing IUD and the levonorgestrel-releasing system, which was introduced in Europe in the early 1990s and in the beginning of this century in the USA.

The introduction of Mirena LNG-IUS has changed the landscape of intrauterine contraception and contributed largely to the revival of the IUD in the United States. It is hardly possible nowadays to think of practicing gynecology without being able to use a LNG-IUS for contraception and/or treatment of the many gynecological conditions for which the LNG-IUS brings relief without having to rely on surgical intervention.

Mirena was, however, not the endpoint as a smaller three-year version, named Jaydess® in Europe and Skyla® in the US (Bayer HealthCare), was also introduced to replace Mirena for use mainly in some young women for whom they deemed a lower release rate of LNG, and a smaller size would be more appropriate. The transverse arm(s) length of Mirena is 32 mm and that of the smaller version is 28 mm. The uterine cavity needs to be sufficiently large to accommodate these devices. Coincidentally, the smaller devices may fit better in smaller uterine cavities that is correct, but then what should we do with the even smaller cavities we see in many young women in our practices today? The average width of the uterine cavity in women, even when the woman has given birth, is 24–25 mm; thus, many women have uterine cavities that are

even narrower.⁵⁹ Our own experience with three-dimensional (3D) ultrasound reveals that a large segment of nulliparous women present with a maximal uterine cavity transverse width of less than 24–25 mm with some smaller than 10 or 15 mm in width. Based on these data, we are convinced that a larger percentage of women, especially younger women, would benefit from a LNG-IUS with a smaller transverse arm(s) (<28 mm) as it may accommodate the narrow cavity better and result in fewer side effects and higher continuation rates than those currently seen in clinical trials.^{8,9,60} Devices with smaller transverse arms are likely better tolerated; however, in women with a large uterus retention maybe a concern. As different IUDs become available, selection of a device, better suited for the patient, will become available. The introduction of office-based 3D ultrasound that would allow direct assessments of uterine cavity shape and size, when coupled with the availability of varied size IUDs, would eventually make patient individualization possible.

Contraceptive efficacy and safety.

Ease and safety of the insertion technique. The new technique of insertion of the T-shaped Femilis LNG-IUS is simple and capable of being performed by various health care providers with minimal training required.⁵⁵ The position of the transverse arm(s) in a descending manner serves to protect against inadvertent perforation of the uterus during insertion.

Contraceptive provision and treatment of frequently occurring gynecological conditions (eg, menorrhagia and anemia) with the LNG-IUS could therefore come within reach of many women, including in women in developing countries who often are obliged to travel to distant hospitals for ineffective conservative treatments or invasive surgery. Given the high effectiveness of LNG-IUS devices, it is imperative to improve access the LNG-IUS to women in developing countries.

Low expulsion rate and spatial compatibility. Low expulsion rates were noted throughout the contraceptive study that

appear attributable to the design features of Femilis 60 LNG-IUS of which the transverse arm(s) is significantly shorter than most other IUDs. A too long transverse arm(s) may not allow sufficient extension in some women with a narrow upper uterine segment. In addition, the slight downward position of the transverse arm(s) contributes to the fundal seeking effect when the uterus contracts preventing downward displacement and expulsion of the LNG-IUS.

The insertion procedure for Femilis is quite different from that utilized in the insertion of the Mirena LNG-IUS (and Jaydess/Skyla), whereby the two arms of the device are retracted in the inserter tube and then released with the transverse arms in an upward arrow-like configuration. During this insertion step, the arms of the Mirena LNG-IUS may not unfold completely, especially when pushed out halfway into the uterine cavity. If the cavity is narrow and the span of the Mirena LNG-IUS is significantly greater than the fundal transverse diameter, pushing the IUS up against the fundus may force the arms to penetrate the fallopian tubes or cause their embedment in the wall(s) of the uterus. This may lead to deep embedment, and even perforation of the uterine wall, or to partial or total expulsion due to forceful uterine contraction (Fig. 4).

Van Schoubroeck et al reported that, in more than 50% of women, apparent embedment was noted on 3D ultrasound measurements only six weeks after insertion of the Mirena LNG-IUS.⁶¹ In our opinion, assessment of a patient's uterine cavity is required prior to the insertion of any framed device. Knowledge of the patient's uterine dimensions and geometry will allow physicians the ability to select devices that are optimal for each patient.⁶² Multiple publications testify to the side effects and complications of gross spatial incompatibility of a framed IUD with the uterine cavity of young and older women.^{63–66}

Long-acting reversible contraception methods have the ability to reduce unintended pregnancy if women continue to use them. Tolerability is paramount to achieve this objective.

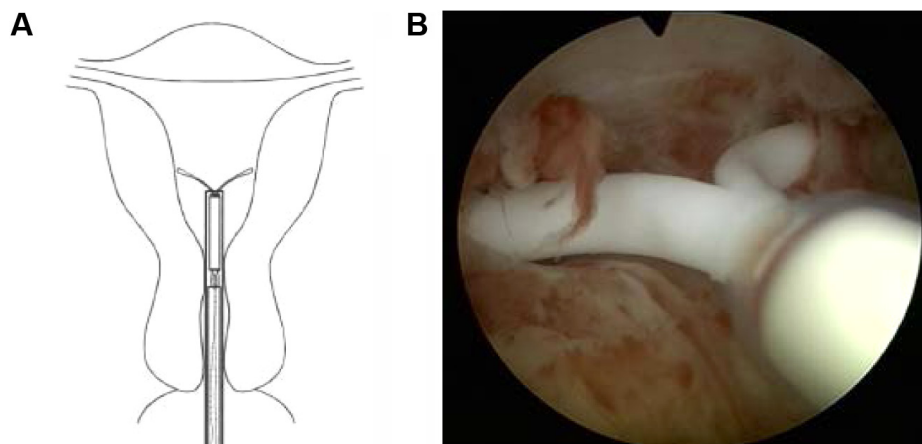


Figure 4. (A) Mirena LNG-IUS uses a different technique than the insertion technique of Femilis. When the LNG-IUS is pushed up against a narrow fundus, the arms may be forced in the fallopian tubes or in the muscular wall. (B) Hysteroscopic example of embedment of both arms in the cornea of the uterus.



Long-term use of the same device is only accomplished if health care providers give attention to the size and shape of the uterine cavity prior to insertion of a *standard size IUD or IUS*. Maximum comfort during the prolonged IUD/IUS use and a high continuation rate can clearly be achieved by using an IUD/IUS of which the greatest transverse dimension of the IUD/IUS is equal or slightly in excess of the fundal transverse dimension.⁶⁷ These geometric relationships promote IUD/IUS retention and stability while minimizing endometrial/myometrial trauma, thereby reducing the likelihood of pain complaints and abnormal bleeding.

Noncontraceptive benefits of LNG-IUS administration. The noncontraceptive benefits of a LNG-IUS for treatment and prevention are recognized by the gynecologist in general, but there is scarce knowledge by the medical community at large about many of the considerable benefits that this method offers beyond contraception. Most women with menstrual problems are treated by their general practitioner with oral contraceptives or progestogens. As these treatments often fail, they are referred to a specialist, often leading to surgical intervention (eg, hysterectomy and endometrial ablation).^{68,69} The first choice, however, should be to administer a LNG-IUS in women with menorrhagia who present to primary care or gynecological providers, as a LNG-IUS is more effective than usual medical treatments in reducing HMB.⁷⁰ Most heavy bleeders can be treated with a LNG-IUS if a pathological condition (eg, fibroids, polyps, and cancer) is absent. Dysfunctional uterine bleeding is usually caused by dysfunction of the corpus luteum in approximately half of women as no significant uterine pathology can be demonstrated in them.⁷¹ In addition, a LNG-IUS provides contraception in these women as a secondary benefit. A study conducted in women with menorrhagia who presented to primary care providers treated with a LNG-IUS concluded that primary care doctors should be encouraged to insert a LNG-IUS in women with this condition. Women fitted with a LNG-IUS are also more likely to be compliant with this treatment.^{72,73}

The difference in amenorrhea rate in the two Femilis MBL studies cannot easily be explained. As one study was conducted in Belgium and the other study in Brazil, it was suggested that geographical or genetic factors may be in play.

Conservative management with LNG-IUS of precancerous changes and early well-differentiated endometrial cancer seems particularly promising in women who wish to preserve their fertility. It is emerging as an alternative to oral progestogens as higher regression and lower hysterectomy rates for the treatment of complex and atypical hyperplasia are achieved with the device.^{74–77} Another benefit is the usefulness of the LNG-IUS in women with adenomyosis and fibromyoma associated HMB.^{78,79}

Furthermore, the combination of intrauterine progestogen delivery to suppress the endometrium, in combination with systemic estrogen, is highly appreciated by women resulting in

a high continuation of use due to the absence of side effects and erratic bleeding in the large majority of women. There are strong arguments to categorize this regimen as probably the most effective, safest, and best accepted route resulting in high patient compliance as well as potentially providing maximal health benefits for peri- and postmenopausal women.⁸⁰

Long-duration of action. Current LNG-IUSs have a lifespan of three to five years. Recent residue studies suggest that the Femilis 60 LNG-IUS has a lifespan of possibly 10 years. The *in vivo* release rate remains constant (zero-order kinetics) over a 10-year period, guaranteeing optimal contraceptive protection.⁵⁴ The long lifespan of the Femilis 60 LNG-IUS may be attractive as it permits women in their late teens to use a single device until they wish to have a child. The mean age at first birth is 26 years in the US with age at first sexual intercourse at approximately 16 years.⁸¹ Women in the EU give birth to their first child at the age of almost 29 years on average, and 40.6% become mothers in their 30s.⁸² These are important aspects women could consider, particularly as unintended pregnancy rates in young women are high and strategies to curb these high rates are not very successful.⁸³ In addition, cost savings would be tremendous as unintended pregnancy is expensive for society.⁸⁴ At the end of the reproductive phase, the LNG-IUS could be highly useful for women over 40 years. In perimenopausal women, the climacteric symptoms, particularly hot flashes, night sweats, sleeping disturbances, and depressive moods, elicited by the decline in circulating estrogens, can cause considerable distress. These are usually more severe in perimenopausal women than in postmenopausal women. Up to 85% of perimenopausal women report suffering from vasomotor symptoms, and their well-being is negatively correlated with the frequency of hot flashes.⁸⁵ The main advantage of a LNG-IUS is probably its predominant local action minimizing or eliminating undesired effects on the protective effects of estrogen. Apart from being an effective and safe contraceptive method, continuously combined estrogen therapy plus a LNG-IUS is a highly practical and beneficial regimen, as it combines the benefits of prevention of endometrial proliferation and treatment of menorrhagia and hyperplasia, if present, together with a suppression of climacteric symptoms. This regimen is also highly recommended in women with risk factors for endometrial cancer.⁷⁴

The method often used in many countries in women towards the end of the reproductive phase is tubal sterilization. In the USA, half of the women aged 40–44 years rely on this method for birth control, but half of the sterilized women would have chosen a reversible effective nonsurgical contraceptive method if the option would have been available.⁸⁶ The proportion of women requesting reversal of sterilization can be as high as 40% in young women.⁸⁷ Although copper-releasing IUDs are an attractive option for many perimenopausal women with no menstrual disturbances, a LNG-IUS has more to offer. In addition to its contraceptive effect, target delivery of LNG reduces menstrual bleeding



and suppresses endometrial growth during estrogen therapy. Women with perimenopausal complaints, using LNG-IUS, can start estrogen therapy as the LNG-IUS will protect the endometrium.⁸⁸

Conclusion

This review suggests that Femilis LNG-IUS, with an average daily release rate of 14 µg of LNG/day over the first five-year life-span, is an effective, well-tolerated, and long-acting contraceptive method. The ease by which the new insertion technique is applied is considered an advantage over the existing insertion techniques of T-shaped IUDs. The shorter transverse arm(s) of the LNG-IUS accommodates better to smaller uterine cavities, although we believe that the development of a 24 mm transverse arm(s) is desirable as many young women have narrow uterine cavities.

This LNG-IUS due to its simplicity and effectiveness opens the way for the use of a LNG-IUS by providers who are less experienced and to women who are underserved and live in remote places in developing countries. Many women, including young and nulliparous women, could substantially benefit from its contraceptive benefits as well as from its ability to treat associated condition such as menorrhagia, avoiding invasive and costly treatment schedules. The long duration of action of the Femilis 60 LNG-IUS may allow many young women the opportunity to postpone pregnancy for prolonged periods. The long-acting Femilis 60 LNG-IUS also provides an opportunity to pass through the transitional perimenopausal period smoothly by adding estrogen therapy when needed allowing them to benefit fully from the advantages that the hormone replacement therapy offers.

Author Contributions

Conceived and designed the experiments: DW, AA. Analyzed the data: DW, AA. Wrote the first draft of the manuscript: DW, NG. Contributed to the writing of the manuscript: DW, AA, NG. Agree with manuscript results and conclusions: DW, AA, NG. Jointly developed the structure and arguments for the paper: DW, NG. Made critical revisions and approved final version: DW, NG. All authors reviewed and approved of the final manuscript.

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