

ORIGINAL ARTICLE

## Why perimenopausal women should consider to use a levonorgestrel intrauterine system

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### Abstract

**Objective:** The use of a levonorgestrel intrauterine system (LNG-IUS) is useful in preventing pregnancy and for the treatment of menstrual disturbances. A smooth or symptom-free transition to and through menopause is possible when LNG-IUS is combined with estrogen therapy. Unfortunately the majority of physicians are generally unaware of this usefulness combined hormonal therapy in the pre-, peri- and postmenopausal women.

**Design and method:** Based on long-term clinical experience with LNG-IUS in the form of Femilis<sup>®</sup>, 104 women were followed from the premenopause through the menopausal transition into the postmenopause. These perimenopausal women received supplemental 17  $\beta$ -estradiol by gel or patch, or orally as estradiol valerate. Patients received one or two separate Femilis insertions at 5 year intervals. Main outcome measures included acceptability and continued use of the combined regimen for the treatment of climacteric symptoms and for prevention of cardiovascular disease, osteoporosis and other adverse effects caused by estrogen deprivation.

**Results:** The average age at insertion was 48 years (range 28–58) and the total duration of use was 137 months (range 80–161). The Femilis LNG-IUS was well tolerated as the number of removals for LNG-IUS-related reasons was low. The LNG-IUS was well retained in the uterine cavity as no expulsions were observed. Seven women were lost to follow-up. Eighty-six women (82%) opted for replacement of an LNG-IUS at expiry after 5 years and continued with the estrogen therapy.

**Conclusion:** Intrauterine progestogen delivery for endometrial suppression in combination with estrogen therapy in the symptomatic perimenopausal women is highly practical as it combines the benefits of prevention of endometrial proliferation and treatment of menorrhagia and hyperplasia, if present. In addition, the contraceptive effect of locally administered LNG is highly desirable as many perimenopausal women run considerable risk of unintended pregnancy. For these reasons, the author views this regimen as one of the most effective, safest and best accepted route resulting in high patient compliance. It is important to convey this message to general practitioners as well as women.

### Keywords

Contraception, EPT, LNG-IUS, menopausal transition, perimenopause

### History

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### Introduction

Prior to the menopause, the great majority of women experience hormonal-related symptoms such as mood changes and sleep disturbances in addition to hot flashes and menstrual irregularities [1]. Hot flashes may even precede menstrual disturbances [2]. Although highly variable between individual patients, fluctuating estrogen levels usually worsen during the menopausal transition and result in anovulatory cycles often associated with heavy menstrual bleeding due to the gradual decrease in luteal progesterone production [3]. Various hormone regimens have been attempted to treat or alleviate the discomfort but compliance remains a burden with oral regimens and oral contraceptives are clearly contraindicated in women over 40 [4]. Although frequently

overlooked, the contraceptive effect of locally administered levonorgestrel (LNG) is highly desirable as many perimenopausal women still run considerable risk of unintended pregnancy [5]. Several review articles have emphasized the non-contraceptive benefits of intrauterine levonorgestrel administration [6–8]. Local treatment with LNG-IUS is attractive as intrauterine administration is simple, well tolerated, and long-lasting while minimizing systemic exposure.

We observed 104 women taking estrogen supplementation and using the Femilis levonorgestrel intrauterine system (LNG-IUS) for an average of ~10 years to control their transition in and through menopause. Typically patients had their IUD replaced at the 5 year expiry with a second device inserted to provide continual hormonal treatment.

### Method

Of the 558 women who participated in a controlled long-term contraceptive study with the Femilis<sup>®</sup> LNG-IUS (APCOR

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Research, Ghent, Belgium), 104 perimenopausal women who developed climacteric symptoms were prescribed systemic estrogen supplementation for relief of their symptoms. The details of the Femilis contraceptive study, including its efficacy and safety, are described elsewhere [9].

The majority of these women were treated with percutaneous 17  $\beta$ -estradiol, 1.5 mg daily (Oestrogel<sup>®</sup>, Besins International, Brussels, Belgium), or an equivalent dose by patch or oral estradiol valerate on a continuous basis. Women continued to be followed at 6 or 12 month intervals over their participation in the study. After expiry of the LNG-IUS, women had the option to stop the estrogen-progestogen (EPT) regimen or to opt for a new LNG-IUS with a lifespan of 5 years.

## Results

The average age women at insertion of the first Femilis LNG-IUS and the average duration of use of the regimen (first and second LNG-IUS combined) are shown in Table 1.

Of the 104 women in the study, all of them received a second LNG-IUS. Following expiry of the second LNG-IUS, on one hand, 86 (82%) opted for replacement of a third LNG-IUS and are continuing to use the combined regimen (Figure 1). Seven women were lost to follow-up, and, on the other hand, the LNG-IUS was removed for various reasons (e.g. 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) (Table 2).

## Discussion

Several reports on the use of the LNG-IUS in perimenopausal women were published earlier [10–15]. Adding estrogen in women requesting relief of climacteric symptoms will enhance their quality of life as the regimen provides satisfactory symptom control and simultaneously avoids any unwanted pregnancy.

Table 1. Patient characteristics (age) ( $n = 104$  perimenopausal/menopausal women in EPT phase) and duration of use until removal of the second LNG-IUS.

	Age (years)	Duration of use (months)
Average	48	137
Range	28–58	80–161



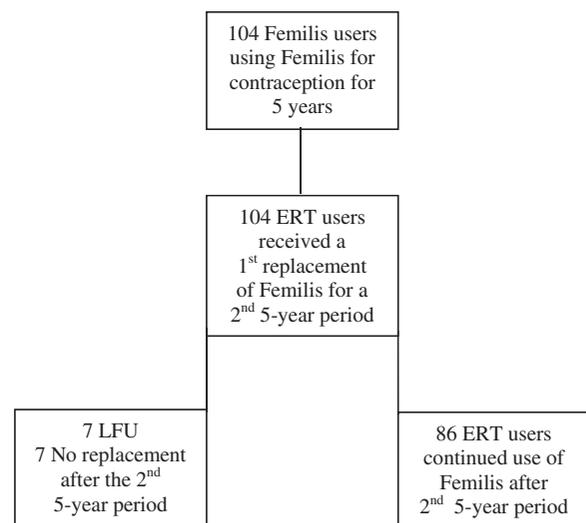
Figure 1. Femilis 60 LNG-IUS is loaded with 60 mg of LNG.

The primary mode of action of local LNG administration is derived from the strong suppression of the endometrium inducing atrophy and decidualization of the stroma. As abnormal uterine bleeding is a frequent gynecological complaint in the perimenopause and increases as women approach menopause, an LNG-IUS will usually stop the dysfunctional uterine bleeding, even if menorrhagic [16]. Dysfunctional uterine bleeding is usually caused by dysfunction of the corpus luteum in approximately half of perimenopausal women as no significant uterine pathology could be demonstrated in 50% among them [17]. Non-atypical and atypical hyperplasia, often found in perimenopausal women, can successfully be treated with LNG-IUS and it is superior to oral progestogen therapy for the treatment of this condition [18,19]. This combined treatment of intrauterine LNG with systemic estrogen supplementation may have a major secondary health benefit as it can replace the need for hysterectomy in many cases [20].

Various combination oral estrogen-progestogen preparations are currently available. A major problem with combined systemic estrogen/progestogen therapy is progestogen-induced premenstrual tension (e.g. mood changes, headache, sleepiness, mastalgia, nausea) [21]. Oral estrogen-progestogens also induce metabolic changes, as evidenced in the WHI study. Progestogens have an essentially anti-estrogenic effect and can potentially counteract the beneficial effects of co-administered estrogens. This is a major concern as the cardioprotective action of estrogens on the arterial physiology could be adversely altered by progestogens in a dose- and duration-dependent manner [22,23]. The advantages of the intrauterine route of administration are substantial as it provides continuous protection of the endometrium and effective treatment of erratic or heavy bleeding simultaneously without exposure to systemic progestogen. This non-systemic progestogen approach, avoiding hormonal side effects, will likely result in high number of women who will continue to use the method necessary to derive long-term health benefits. In women using conventional estrogen/progestogen combinations, sequential or continuous combined regimens, erratic breakthrough bleeding has been reported to be as high as 64% and is the major reason to discontinue the method in over 30% of women [24].

This current study was conducted in women who requested insertion primarily as a contraceptive methodology. As time progressed and women started to develop menopausal-related

Table 2. Summary of results in 104 ERT starters.



climacteric symptoms, systemic estrogen supplementation was instituted. The combined therapy served to reducing or eliminating complaints in the majority of women. When the LNG-IUS needed replacement after its 5 year life-span, a second LNG-IUS was easily inserted. A third LNG-IUS was inserted in 82% of women. The simplicity, effectiveness, and safety of the regimen, as well as the fact that women were already used and were highly confident about the method, explains the high continuation of use. About 7% of women were lost to follow-up and may not have opted for a new LNG-IUS, from this we can conclude that the regimen is highly accepted.

The obvious limitation of this study is its small sample size. This is counteracted by the high number of women who wished to continue the regimen.

### Declaration of interest

Dirk Wildemeersch, MD, PhD, has conducted research in the field of non-hormonal and hormonal, framed and frameless intrauterine devices for 30 years. The author alone is responsible for the content and writing of this paper.

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