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REVIEW ARTICLE

Safety and comfort of long-term continuous combined transdermal estrogen and intrauterine levonorgestrel administration for postmenopausal hormone substitution – a review

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Abstract

Objective: To review the endometrial safety and patient acceptability of long-term use of continuous transdermal estrogen substitution combined with intrauterine release of levonorgestrel (LNG) in postmenopausal women.

Design: One-hundred and fifty-three women who utilized the regimen for 2 IUD cycles were followed-up for a period of 10 years. Histology of the endometrium was evaluated at the end of this period to assess endometrial safety and the acceptability of the method was assessed based on the replacement rate of the LNG-IUS and continuation of ET.

Results: The regimen, administered over a 10-year period, was very well tolerated and the IUD was retained well and no expulsions occurred. The dominant endometrial histologic picture was that of inactive endometrium characterized by glandular atrophy and stroma decidualization (Kurman classification 5b). No cases of endometrial hyperplasia were found.

Conclusion: The low systemic absorption of LNG could be desirable, thus allowing for maximization of the beneficial effects of ET on organ tissues (e.g. cardiovascular tissues and breast). Repeat LNG-IUS is associated with high patient satisfaction. If started before the age of 60, this regimen could be advised for lifelong prevention of cardiovascular disease and other prevention measures. The LNG-IUS was shown to effectively oppose the secondary effects of systemic estrogen on the endometrium tissue resulting in strong suppression during the entire period of EPT.

Keywords

Acceptability, endometrial histology, endometrial suppression, estro-progestogen therapy, estrogen therapy, intrauterine drug delivery system, levonorgestrel, tolerance

History

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Introduction

There is no disputing the therapeutic benefit to postmenopausal women of estrogen. Reduction in cardiovascular disease, stroke, mental function have all been attributed to the presence of estrogen. Unfortunately, the Women's Health Initiative (WHI) study [1] and the Million Women Study (MWS) [2] showed an increase in breast cancer, cardiovascular disease, and venous thromboembolic events among postmenopausal estro-progestogen therapy (EPT) users. This was largely publicized in the media which resulted in a dramatic decrease in the use of estrogenic menopausal hormone therapy [3]. However, during the intervening years following the publication of the WHI study, new evidence was presented which placed these initial findings into perspective [4–6]. The most important findings were that overall mortality, myocardial infarction and heart failure were significantly reduced when EPT was initiated close to menopause [7,8]. This period was termed ''window of opportunity''. Several large observational and randomized trials all confirm the timing hypothesis [9]. The WHI and MWS studies heightened women's fear of the development of breast cancer with systemic estrogen use. However, further research suggests that the risk of breast cancer with estrogenic supplementation is non-conclusive and may even be decreased with the use of estrogen only therapy [10,11]. Lifestyle factors such as obesity, immobility and unhealthy food intake may have more impact on the risk of breast cancer than EPT. In addition, women using ET alone have a significant decrease in breast cancer risk. It was also found that the risk of thromboembolism could be reversed if transdermal ET was used instead of oral ET therapy [12]. The occurrence of stroke was also influenced by the route of administration of ET. Some observational studies suggest that transdermal ET confer a lower risk compared with oral ET [13]. Estrogen has been shown to be protective in stroke particularly in younger women [14].

Progestogen administration is essential to prevent the endometrium from becoming neoplastic [15]. Oral progestogen added to ET has been shown to modify cholesterol metabolism in a negative way, together with an increased risk of cardiovascular disease making this route of administration, for certain progestogens at least, less appropriate [16]. Treatments and delivery systems which allow for the positive and protective effects of progestogen administration but without marked systemic effects are needed. The use of levonorgestrel intrauterine system (LNG-IUS) delivers LNG locally to the target cells of the endometrium causing a profound suppressive effect on endometrial growth rendering the endometrium inactive. Additionally, intrauterine delivery of LNG eliminates uterine bleeding while having minimal systemic exposure [17]. The present paper reports on the long-term assessment of endometrium safety for up to 10

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years, after initiation of the continuous combined regimen of systemic estrogen supplementation along with intrauterine LNG administration in 153 postmenopausal women, as well as the acceptability of the regimen.

Materials and methods

Patients

A total of 242 postmenopausal women used the combined regimen consisting of systemic estrogen and the Femilis Slim LNG-IUS. Of this population, 153 women entered into an extension of the study and were fitted with a second 5-year device thus receiving two Femilis Slim LNG-IUS in succession. This report is a continuation of earlier reports published and evaluates the findings of the women who continued for a total of approximately 10 years [18,19].

Levonorgestrel-releasing intrauterine systems

Figure 1 shows the small T-shaped LNG-IUS in comparison with the much larger Mirena LNG-IUS (Bayer Healthcare, Berlin, Germany). The initial release rate is approximately 20 μg/day averaging 14 μg/day over its 5 year lifespan.

Admission

One hundred and fifty-three women were enrolled in the study. The majority (~90%) received percutaneous 17β estradiol gel, 1.5 mg daily (Oestrogel®, Besins International, Brussels, Belgium), or an equivalent dose by patch or oral estradiol valerate (10%), on a continuous basis. Femilis Slim LNG-IUS was inserted in the uterus to establish endometrial suppression and prevent hyperplasia. The use of the levonorgestrel-releasing drug delivery system was approved by the Ethics Committee of the University in Ghent, Belgium. Written informed consent was obtained. The insertions were performed in a private practice setting and were done without or with local intracervical anesthesia.

Follow-up

Women were followed-up at 1, 3, 6, 12 months and 6-monthly following insertion of the LNG-IUS and yearly after insertion of the second LNG-IUS. The initial estrogen dose over the total observation period remained constant in most women. In a few women the startup dose of 1.5 mg 17β estradiol gel daily, or an equivalent dose by patch or orally, was reduced because of side effects (e.g., breast tenderness) or concern about the safety of postmenopausal therapy in general caused by the adverse publicity, alleging an increased risk of breast cancer with estrogen–progestogen therapy, following the publication of the Women's Health Initiative study in 2002. The normal dose of 1.5 mg 17β estradiol gel daily, 50 μg patches twice per week or 2 mg estradiol valerate/d orally was resumed as soon as possible.

After expiry of the second Femilis Slim LNG-IUS, the LNG-IUS was removed and an endometrium sample was taken with a suction curette (i.e., Probet®, Gynétics, Belgium). The samples were drawn from all parts of the uterus to get a representative sample. The biopsies were placed in phosphate-buffered formaldehyde 4% immediately upon collection and stained with hematoxylin and eosin for examination. Examination was done according to the diagnostic criteria of Hendrickson et al [20]. The endometrial samples were classified according to Kurman [21]. A new LNG-IUS was inserted if the women wished to continue the preventive EPT therapy.

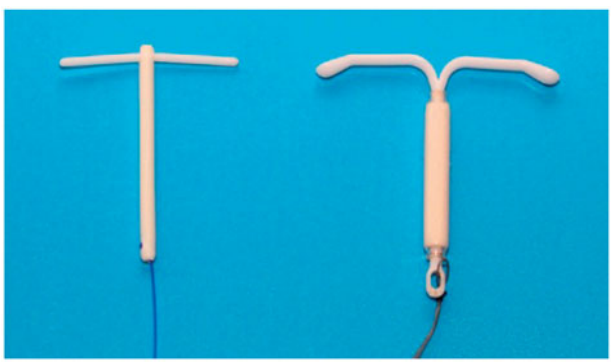


Figure 1. Femilis® Slim LNG-IUS (left) with 24 mm transverse arm and 2 mm wide drug delivery rod; Mirena® LNG-IUS (right) with transverse arm length of 32 mm.

Results

Insertion was simple in the majority of women as the inserter tube is only 3 mm in diameter with the procedure itself being simple and rapid as described previously [18]. Following initiation of the ET plus LNG-IUS regimen, menopausal symptoms subsided and improvement or absence of symptoms was usually maintained throughout the EPT. At expiry of the first LNG-IUS, 153 women received a second Femilis LNG-IUS as part of the study. By combining the follow-up periods of both LNG-IUSs, a median duration of use of approximately 8–10 years of follow-up was obtained.

The median age at insertion was 55 years (range 39–72) and the median duration of use of the regimen was 102 months (range 39–171) (Table 1). Table 2 shows the number of women in the total group, the number of women fitted with a 2nd LNG-IUS (extended study) and the number of women opting for a third LNG-IUS at the end of the extended study period. Prior to inserting the third LNG-IUS, a pipelle biopsy was taken. One hundred and forty-eight pipelle biopsies were performed. The dominant endometrial histological picture was that of epithelial atrophy accompanied by decidualization of the stroma (Kurman classification 2 + 5b; 5b; 2 or 3). In 13 women, only very scanty tissue could be obtained during the last sampling due to profound endometrial atrophy (Kurman classification 1). In 2 women no tissue could be obtained probably due to extreme epithelial atrophy. No endometrial hyperplasia was found.

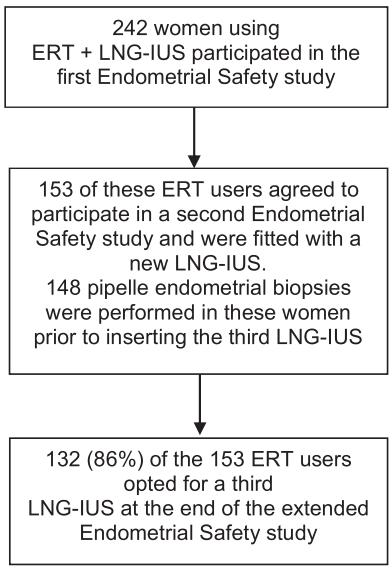
Typically, women were completely bled free after the first days, rarely weeks, especially if they had used an LNG-IUS before. Adverse events during the first year were minor such as mood swings which occurred in less than 1%. Furthermore, other symptoms (e.g., migraine, vaginal discharge, breast tenderness, dyspareunia) occurred in approximately 5% of women.

One hundred and thirty-two women (86%) requested a third replacement of the LNG-IUS, indicating the high acceptability and convenience of use of the regimen. In 15 women (10%), no replacement was done for various reasons (e.g., moved to another place (3), hysterectomy for uterine prolapsus (2), cancer of the breast (4) and kidney (1), unrelated death (1), fear for breast cancer, no need for or misinformation about hormones (3), and

Table 1. Patient characteristics (age) and duration of EPT use.

	Age (years)	Duration of use (months)
Median	55	102
Range	39–72	39–171

Table 2. Patients fitted with three consecutive LNG-IUS in combination with EPT.



financial issues as women had to pay for the new LNG-IUS (1)). Only 4% of women were lost to follow-up.

Discussion

Cardiovascular disease (CVD) is the leading cause of death in women. In Europe, 22% of women die from coronary heart disease (CHD) alone, and 52% of mortality in European women is due to cardiovascular disease (including CHD, stroke and other CVD). Cancer is the cause of death in 18% of all European women, and breast cancer accounts for 3% of the total number of deaths [7]. As estradiol dilates the coronary arteries and increases cerebral perfusion, it may be advisable for women without uterus, and for women using a LNG-IUS (probably also for women using micronized progesterone or dydrogesterone), to continue ET as long as possible as it may prevent cardiovascular events. In addition, women should be informed that, particularly younger postmenopausal women <60 years of age, who discontinue ET are vulnerable to cardiac and stroke as this may result in vasoconstriction of the arteries [22].

All the detrimental effects reported in the WHI and MWS may not be solely attributable to the use of estrogen. Oral progestogen added to ET has been blamed to blunt the beneficial rise in HDL-cholesterol seen with estrogen supplementation. Epidemiological studies also suggest an increase in breast cancer, cardiovascular disease, and venous thromboembolic events among postmenopausal EPT users, which may be attributed to the progestogen component although the underlying mechanism has not yet been fully elucidated [23]. As the increase in breast cancer was not present in long-term users of estrogen-only therapy (a slight increase was seen in the MWS), it was concluded that the increased incidence of breast cancer was attributed to the progestogen component of the EPT regimen [24]. In addition, the type of progestogen plays a role in the risk of breast cancer as on the cardiovascular system [25]. This indicates the need for the development of safer progestogens or alternative routes of administration to avoid the adverse effects on the breast and cardiovascular system.

A levonorgestrel intrauterine system (LNG-IUS) that delivers low but constant amounts of LNG to the target cells of the endometrium causes a strong suppressive effect on endometrial growth rendering the endometrium inactive, while plasma levels are low [17]. These low plasma levels and resulting minimal systemic exposure can have a significantly lower impact on the breast and cardiovascular tissue.

The first clinical experiences with the Femilis Slim LNG-IUSs in postmenopausal women using EPT were published previously [18,19]. The current extended study confirms the high acceptability, comfort and convenience of use of the EPT regimen. A large number of women requested continuation beyond the original 5-year lifespan, notwithstanding the fact that most women did not have hot flushes and other climacteric symptoms anymore. Women were generally highly pleased with the treatment regimen and its benefits, including the intrauterine device, thereby requesting a third device be inserted.

The use of smaller LNG-IUS device with high uterine compatibility is an important component when treating postmenopausal women. The reduction in uterine size in postmenopausal women is related to years since menopause and many women have an extremely small uterus [26]. Beyond the differences in size between the Femilis Slim IUS and the Mirena LNG-IUS, the insertion procedure and inserter tube are much simpler and faster to use, which minimizes patient discomfort [18]. A review by Riphagen on the use Mirena LNG-IUS in postmenopausal women showed that the Mirena LNG-IUS was easy to insert in only 46–90%, and cervical canal dilatation and/or local anesthesia was necessary in 25% of insertions in postmenopausal women [27]. Remarkably, uterine cramps, often seen in young IUD users, caused by IUD-uterine cavity spatial discrepancy, did not occur in virtually all women in this study. The quiescent state of the postmenopausal uterus and the smaller size of the IUD used are probably the reason for the absence of complaints.

The study has some limitations as to its design and anecdotal nature, but the extended duration of exposure, the nature and the reasonable size of the study population support its relevance. The strength of this study is the finding that all women had a negative endometrial biopsy consistent with the absence of endometrial hyperplasia and resulted in endometrial atrophy. The participants viewed the treatment as valuable with a large percentage (>85%) requesting continuation with a third LNG-IUS, even at their own expense.

Conclusion

Continuous, intrauterine progestogen delivery could be the ideal and safest route of administration as this report indicates. If started early in menopause, (preferably around the age of 50), this regimen could be advised for lifelong prevention of cardiovascular disease and other prevention measures, which is in contrast with current guidelines that recommend hormone therapy for the shortest possible time [28].

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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 for contraception and treatment. He assisted in the development of the Femilis® LNG-IUS. He did not receive any financial compensation of any kind for this study. The author alone is responsible for the content and writing of this paper.

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