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Endometrial safety after 5 years of continuous combined transdermal estrogen and intrauterine levonorgestrel delivery for postmenopausal hormone substitution

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Abstract

Objective: To investigate endometrial histology and thickness of the endometrium after long-term use of continuous transdermal estrogen substitution combined with intrauterine release of levonorgestrel (LNG) in postmenopausal women.
Design: A 5-year non-comparative prospective clinical trial.
Subjects: Out of 182 symptomatic postmenopausal women using estrogen substitution therapy (EST) combined with a novel T-shaped LNG-releasing intrauterine system (Femilis™ Slim LNG-IUS), to prevent endometrial proliferation and bleeding, only those women ($n = 102$) who used two consecutive LNG-IUSs, were isolated with the aim to study the long-term effects on the endometrium. The mean age of the women was 57 years (range 47–71). The majority of women received percutaneous 17β estradiol, 1.5 mg daily, or an equivalent dose by patch or orally, on a continuous basis.
Main outcome measures: Endometrial histology and ultrasonographic evidence of endometrial suppression, after a period of approximately 5 years of use. The mean duration of use of the regimen was 70 months (range 25–98).
Results: 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. On transvaginal ultrasound, this corresponds with a thin endometrium ($\leq$5 mm).
Conclusion: The results of this 5-year study in 102 postmenopausal women using EST demonstrates that the LNG-IUS effectively opposes the estrogenic effect on the endometrium resulting in strong suppression during the entire period of EST. Due to its high efficacy and absence of systemic effects on organ tissues (e.g., breasts), target delivery in the uterine cavity could be a preferred route to administer a progestagen in women using EST.

Keywords: Intrauterine drug delivery system (IUS); Levonorgestrel; Hormone substitution therapy (HST); Endometrial suppression; Endometrial histology; Endometrial thickness

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1. Introduction

Since the mid seventies it is well known that the addition of progestagen to EST is necessary to prevent the endometrium from becoming neoplastic [1–3].

Oral progestagen, added to EST has been shown to modify cholesterol metabolism in a negative way, together with an increased risk of cardiovascular disease [4]. The Women's Health Initiative (WHI) study [5] and the Million Women Study (MWS) [6], showed an increase in breast cancer, cardiovascular disease, and venous thromboembolic events among postmenopausal HST users. 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 progestagen component of the HST regimen [7]. An intrauterine system which delivers a progestagen direct to the uterus would minimize or eliminate the impact of the hormone on breast and other organ tissues [8,9].

A levonorgestrel intrauterine system (LNG-IUS) delivers LNG to the target cells of the endometrium which causes a profound suppressive effect on endometrial growth rendering the endometrium inactive and, simultaneously eliminating uterine bleeding [10,11]. Pharmacokinetic studies with a 20 μg releasing LNG-IUS (Mirena®, Schering AG, Germany) have shown plasma concentrations which are substantially lower than those seen with subdermal levonorgestrel implant (Norplant®), the combined oral contraceptive and the mini-pill and, unlike the oral contraceptives, the levels with Mirena do not display peaks and troughs [12]. These low plasma levels may have a significantly lower impact on the breast and cardiovascular tissue.

Previous reports, using a "frameless" LNG-IUS (Fibroplant™, Contrel Research, Ghent, Belgium), releasing 14 μg of LNG/d, and a T-shaped LNG-IUS (Femilis™ Slim, Contrel Research, Ghent, Belgium), releasing 20 μg of LNG/d, suggested that the intrauterine systems are easily inserted, well tolerated and that the intrauterine levonorgestrel release protects the endometrium during estrogen substitution [13–16]. However, most of these studies were limited in duration and in number of patients. The present paper reports on the long-term assessment of the endometrium, up to 8 years after initiation of the continuous combined regimen, in 102 postmenopausal women.

2. Materials and methods

2.1. Patients

A total of 264 postmenopausal women used the combined regimen consisting of parenteral estrogen and a LNG-IUS, either the frameless Fibroplant LNG-IUS or the T-shaped, Femilis Slim LNG-IUS. Of this population, only the women who used the frameless LNG-IUS and the T-shaped LNG-IUS in succession, after expiry and removal of the first LNG-IUS, were entered into the study. One hundred and two women were identified who constitute the 'long-term' group. Women with prior endometrial hyperplasia were excluded from the study.

2.2. Levonorgestrel-releasing intrauterine systems

Both systems have been described previously in this journal [9,12]. Whilst Fibroplant LNG-IUS has no frame and requires anchoring to the uterine fundus to prevent expulsion, Femilis Slim LNG-IUS, on the other hand, is a T-shaped IUS similar to the conventional copper-T intrauterine device (IUD).

2.3. Admission

Only postmenopausal women with severe climacteric symptoms were enrolled in the study ($n = 102$). The majority ($n = 70$) received percutaneous 17β estradiol, 1.5 mg daily (Oestrogel®, Besins International, Brussels, Belgium), or an equivalent dose by patch or orally, on a continuous basis. The remaining group of women ($n = 32$) used a lower dose on their own initiative. An intrauterine frameless LNG-IUS was inserted 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. Prior to the insertion procedure, a medical history was taken, together with a general health check-up and a pelvic examination. Since women included in the study were at low risk for sexual transmitted diseases (STDs), no