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Treatment of non atypical and atypical endometrial hyperplasia with a levonorgestrel-releasing intrauterine system

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Condensation
The results suggest that the "frameless" 14 μg/d releasing FibroPlant-LNG system is an effective method to treat women with non atypical and typical hyperplasia.

Abstract
Objective: A "frameless" intrauterine drug delivery system releasing 14 μg/d of levonorgestrel (LNG) was used to treat non atypical and typical endometrial hyperplasia in 12 women.
Study design: Non-comparative study with up to 3 to 4 years follow-up.
Results: The cure rate was 100% as confirmed by repeat endometrial biopsy.
Conclusion: This method could be considered an alternative to hysterectomy.

Keywords: "Frameless" intrauterine system (IUS), levonorgestrel, endometrial hyperplasia, pilot study

Introduction
An alternative route to administer potent progestogens to render the uterine tissues incapable of responding to estrogen stimulation is to use an intrauterine drug delivery system. Locally acting progestogens act many times stronger on the endometrium than when given systemically. Dosage can, therefore, be reduced significantly, minimizing side effects and optimizing patient compliance.
Clinical studies with a "frameless"-levonorgestrel (LNG) intrauterine system (IUS), releasing 14 μg of LNG per day, suggest that the IUS is effective to provide strong endometrial suppression which accounts for its endometrial suppressive effect during estrogen replacement therapy (ERT), its effect on menstrual blood loss as well as its contraceptive action.[1] In addition, the "frameless" design characteristics of the LNG IUS account for minimising the occurrence of complaints of pain and expulsion. Moreover, the low daily release results in a low incidence of hormonal side effects.
The purpose of the present study was to evaluate if the longacting LNG IUS could be used for the treatment of hyperplasia and prevent recurrence.

Material and Methods

The drug delivery system consists of a non-resorbable thread of which its proximal end is provided with a single knot. Attached thereto is a 4-cm long and 1.2 mm wide fibrous delivery system, releasing approximately 14 μg of LNG per day. The anchoring knot is implanted into the myometrium of the uterine fundus using an insertion instrument, so permanently securing the implant in the uterine cavity. Since the LNG IUS has no frame, it is completely flexible, adapting to cavities of every size and shape (Figure 1).

Women with abnormal uterine bleeding and with endometrial hyperplasia, confirmed by pipelle biopsy, received the LNG IUS for local treatment of the condition. Written informed consent was obtained and the use of the LNG IUS for preclinical trials was approved by the Ethics Committee of the Ghent University Hospital. Prior to the insertion procedure, all women were screened for their clinical suitability for IUS insertion and compliance with the WHO eligibility criteria. Following insertion, women were followed-up at 1, 3, 6,12 months following insertion of the IUS and 6-monthly thereafter. Monitoring of the endometrium during treatment was conducted by transvaginal ultrasound (TVU) and by repeat endometrial biopsy in the cases with atypical hyperplasia after 1 to 3 years.

Patients

Twelve healthy women (eleven parous and one nulliparous) with age ranging from 46 to 67 years of age were included in the study. Hypertension and diabetes was not present in any of them. Eight women developed postmenopausal bleeding as a result of unopposed estrogen stimulation for ERT, after having taken the medication for at least 6 months up to approximately 2 years. One woman consulted because of abnormal bleeding during tamoxifen treatment for breast cancer. Three other women had abnormal premenopausal bleeding. The histopathological diagnosis (WHO classification) was 'non atypical (simple) hyperplasia' in 7 women and 'atypical hyperplasia' in 5 women (adenomatous hyperplasia with atypia in three of them). In one of the latter patients an invasive well-differentiated adenocarcinoma was found but this was not confirmed in two subsequent endometrial pipelle samplings.

Results

After an initial short period of spotting, bleeding stopped in all women studied. All women developed a thin endometrium (< 5 mm in thickness), as assessed by transvaginal ultrasound, except patient No.12. The latter patient presented with a polypoid structure of 20 mm in diameter prior to treatment which diminished in size to 8 mm after 12 months with no abonormal bleeding. All women, including women with atypical hyperplasia were considered to be cured, which was confirmed by repeat endometrial pipelle biopsy performed after a treatment period of 12 months. In the woman with the initial diagnosis of endometrial carcinoma, three pipelle biopsies were performed to confirm absence of carcinoma. Eight of the 12 women in the study resumed ERT. All women are continuing in the study and have no complaints nor side effects. The high tolerance is attributed to the frameless design characteristics of the intrauterine system.

Comments

In recent years, endometrial hyperplasia is caused most often by use of unopposed estrogen for ERT and tamoxifen for the treatment of breast cancer. Non atypical (simple) hyperplasia is usually treated by oral administration of progestogens in sufficient dose and duration. However, if the treatment is discontinued, recurrence may occur. Locally applied delivery of levonorgestrel is much more potent than oral treatment and it is, therefore, logical that this form of treatment should be preferred to oral and also to surgical treatment if it could be shown to be effective. An implantable method also provides better patient compliance.

The preferred treatment for adenomatous hyperplasia with atypia or adenocarcinoma of the endometrium is hysterectomy. However, successful treatment of early endometrial carcinoma has been reported with a 65 μg/d progesterone-releasing IUS, followed-up to 36 months, but, results of biopsies were negative only in 7 of 11 at 6 months and 6 of 8 at 12 months.[2] Oral progestin treatment has also been successful for the conservative treatment of atypical hyperplasia. However, the patient must be prepared to comply with prolonged treatment which is difficult for many women.[3] Target delivery of levonorgestrel acts much stronger on the endometrium than intrauterine progesterone delivery and oral progestin treatment. Besides, the treatment is continuous and compliance is not an issue which may explain the excellent results obtained in the present study.

Conclusion: The results suggest that the LNG system, releasing 14 μg of LNG per day, is an effective method for suppressing the endometrium in women with non atypical and typical hyperplasia and constitutes an alternative to hysterectomy on condition that women can be properly followed-up.

References

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FIGURES

Figure 1. The FibroPlant-LNG intrauterine system after insertion in a uterine model.