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CLINICAL ARTICLE

# Letrozole as primary therapy for endometrial hyperplasia in young women

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Aromatase inhibitor;
Letrozole;
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**Abstract**

*Objective:* To study letrozole as a primary therapeutic agent for endometrial hyperplasia with or without atypia in young women. *Methods:* Five premenopausal women presenting for infertility were diagnosed as having endometrial hyperplasia. A second biopsy was performed after they were treated for 3 months with 2.5 mg of letrozole per day. Serum levels of estradiol and progesterone were measured each month. *Results:* Curettage of the endometrium at the end of treatment revealed no evidence of endometrial hyperplasia or atypia in any of the patients. Low serum levels of estradiol were found in all patients. *Conclusion:* This case series indicates that aromatase inhibitors deserve attention for the conservative treatment of endometrial hyperplasia. However, more studies are needed to confirm the efficacy and safety of this agent.


## 1. Introduction

Endometrial hyperplasia is an estrogen-driven disease. Antiestrogen treatment with progestins [1] or estrogen deprivation with gonadotropin-releasing hormone agonists have been shown to reverse endometrial hyperplasia [2]. However, several reports have emphasized the potentially unfavorable vascular effects of progestins [3] as well as elevated lipid and lipoprotein levels [4]. Progestin treatment can also result in weight gain and mood changes [5]. Treatment with agonists of gonadotropin-releasing hormone has been found to have the same vasomotor and osteoporotic effects as hypoestrogenic treatment [6].

Letrozole is an aromatase inhibitor that suppresses estrogen biosynthesis. It is currently administered to postmenopausal women with advanced breast cancer to reduce estrogen production due to peripheral aromatization of androgens. In one study, administering up to 5 mg of letrozole per day for 2 weeks produced a marked suppression of estradiol, estrone, and estrone sulfate production, with very few adverse effects [7,8].

Higher aromatase levels have been reported in hyperplastic than in normal endometria [9]. Furthermore, the expression of aromatase is even higher in atypical hyperplastic endometria than in hyperplastic endometria without atypia [9]. The intratumoral biosynthesis of estrogens is considered to play a role in endometrial cancer development

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and progression [10,11]. It has been speculated that aromatase inhibitors might reduce local biosynthesis of estrogen in the endometrium.

We report the outcomes for women who wished to become pregnant and were treated with letrozole for endometrial hyperplasia with or without atypia.

## 2. Materials and methods

Institutional review board approval was obtained for this study. Five premenopausal women presented to our center between April and September 2006 for infertility. Their mean age was 32.6 years (range, 27–38 years) and mean BMI (calculated as weight in kilograms divided by the square of height in meters) was 24.9 (range, 20–28). Of these, 4 had secondary amenorrhea and were diagnosed as having polycystic ovary syndrome, their only cause of infertility. The remaining patient had obstructed fallopian tubes. One patient had irregular bleeding after being amenorrheic for 6 months. Amenorrhea was defined as the absence of menstruation for at least 6 months or for a length of time equivalent to at least 3 times that of the previous cycle.

The 5 patients were given whole-wall endometrial curettage because of irregular uterine bleeding or a thick endometrium on ultrasound, and endometrial hyperplasia was histologically diagnosed in all 5 (3 had complex hyperplasia without atypia, 1 had simple atypical hyperplasia, and 1 had complex atypical hyperplasia). They were given 2.5 mg of letrozole daily for 3 months. None of the women was taking hormonal therapy. One had well-controlled arterial hypertension. During treatment, all women were followed up by interview and transvaginal ultrasound. Blood sampling was performed every month to measure serum levels of estradiol and progesterone. Biopsies were repeated in all patients at the end of the 3-month treatment. Contraception with condoms was advised during treatment.

All women were counseled by an experienced gynecologist and they all provided valid informed consent before entering the study.

## 3. Results

All 5 women completed their 3-month treatment with letrozole. Their mean (range) endometrial thickness was 1.16±0.30 cm (1.0–1.7 cm) before treatment and 0.94±0.13 cm (0.8–1.10 cm) after treatment.

When curettage was performed at the end of treatment, 3 patients had a proliferative and 2 had a secretory endometrium, with no evidence of endometrial hyperplasia or atypia. The 4 patients with secondary amenorrhea had 1 or more menstruations during treatment. The patients had low estradiol levels all during treatment (range, 73.0–166.0 pmol/L), and their progesterone levels were between 1.2 and 139.6 nmol/L. No adverse effects or irregular vaginal bleeding were reported after treatment initiation.

## 4. Discussion

The results of this study show that premenopausal women with endometrial hyperplasia with or without atypia can be successfully treated with letrozole alone. Although this report concerns only a few cases, it provides a promising method for the conservative treatment of endometrial hyperplasia in premenopausal women.

A study reported on the efficacy of anastrozole, an aromatase inhibitor, in the treatment of obese postmenopausal women having endometrial hyperplasia with or without atypia [12]. Burnett and colleagues [13] also found that the combination of progestin and anastrozole might be more successful than progestin alone for the conservative management of well-differentiated endometrial cancers in obese premenopausal women. Obesity is the most common and significant risk factor for the development of endometrial hyperplasia and endometrial cancer. Androgens are converted into estrogens by aromatase, an enzyme mainly expressed in adipose tissue [14].

In this study, the 3 nonobese patients (BMI<27.3) responded well to letrozole treatment. Low serum levels of estradiol were detected in all patients. In premenopausal women, ovaries are the main source of estradiol [15]. Our study suggests that letrozole can reduce circulating estrogen levels in premenopausal women who are not obese, and therefore may have a role to play in the inhibition of endometrial hyperplasia.

It was interesting that the 4 patients with secondary amenorrhea had 1 or more menstruations during the 3-month treatment. This suggests that continuous administration of letrozole in premenopausal women may induce ovulation, thereby leading to the production of progesterone, which plays an important role in inhibiting endometrial hyperplasia. Because the patients' blood was sampled each month after treatment initiation, rather than according to follicular development, we found high levels of progesterone in only 3 women; such levels, however, confirmed that ovulation was occurring in these women. In 2 studies by Mitwally and Casper [16,17], a single administration of 20 mg of letrozole or the daily administration of 2.5 mg of letrozole for 5 days induced ovulation.

Whether aromatase inhibitors reduce estrogen synthesis in the endometrium needs to be investigated.

This case series indicates that aromatase inhibitors deserve attention for the conservative treatment of endometrial hyperplasia in young women who wish to become pregnant. However, the success of this kind of treatment should be evaluated after a minimum of 24 months of follow-up [2]. In this study the follow-up time was too short and needed to be extended. More experience is required before aromatase inhibitors can be accepted as safe and effective for the medical management of endometrial hyperplasia.

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