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Comparison the Effect of Letrozole Versus Medroxy Progesterone Acetate on Premenopausal Patients With Endometrial Hyperplasia: An Randomized clinical trial

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Abstract

Objective: The assessing the effect of letrozole and medroxyprogesterone acetate on women with simple endometrial hyperplasia without atypia in reproductive age.

Material and Methods: Eighty patients of Abolfazle clinic in Bushehr with abnormal uterine bleeding and simple endometrial hyperplasia enrolled in this study. The patients were randomized in 2 groups: group A included 40 patients who received 10 mg medroxyprogesterone acetate for 10 days in each month during 3 months and group B included 40 patient that received 2.5 mg letrozole for 3 months. Serial transvaginal sonography and estradiol were checked basically and repeated after 3 months of treatment. Main outcome measures were endometrial thickness and estradiol level in serum.

Results: In 2 groups A & B, there were no significant differences in the base variables. The level of estradiol in groups A and B before treatment was similar in the 2 groups. Endometrial thickness in groups A and B was not statistically significant. The difference between these 2 groups from the endometrial thickness reduction viewpoint, is not significant (P value = 0.445). The level of decline estradiol in serum in the groups A&B was significant,

Conclusion: Letrozole is an acceptable drug for treatment of simple endometrial hyperplasia especially in the patients who did not tolerate medroxyprogesterone.

Keywords: Letrozole, progesterone, endometrial hyperplasia, estradiol.

Introduction

An abnormal bleeding which occurs in an unlimited time of the menstrual cycle is called abnormal uterine bleeding. This type of bleeding needs to be investigated in all ages, especially before menopause. After ruling out the organic causes, the most common cause of abnormal uterine bleeding is anovulation and subsequently, the endometrial hyperplasia (1,2). The term endometrial hyperplasia explains the spectrum of combined effects of endometrial glands and stroma, and these conditions are usually observed during the investigation of abnormal bleeding and its frequent treatment (3,4). The irregular bleeding leads to some problems such as anemia, marital problems, infertility, and an increased risk of endometrial cancer; therefore, patients should follow the duration of their treatment seriously due to the fear of cancer. Endometrial hyperplasia is an estrogen-dependent disease caused by internal and external hormones (3,5).

Hyperplasia is usually caused by the proliferative endometrium and long stimulation of estrogen in the absence of progestin (6). This disease has 2 kinds, which are known as simple and complex kinds, and each of them can exist with atypia or without atypia. The risk of progression towards cancer in simple and complex hyperplasia is 1% and 3%, respectively. Moreover, the simple and complex hyperplasia with atypia (presence of nuclear enlargement, the chromatin may be either evenly dispersed or clumped) increases the risk of cancer progression up to 8% and 29%, respectively (7).

The significance of all kinds of hyperplasia diseases is due to the fact that they cause the abnormal bleeding, and they occur before cancer or simultaneously with cancer (7).

Estrogen is one of the important hormones present in the body of women, and is secreted by the ovaries before menopause (6). One of the most common and important factors that determines the progress of endometrial hyperplasia is overweight which results in endometrial cancer. Endogen changes into estrogen by aromatase in peripheral tissues; this enzyme is stored in the adipose tissue.

Anti-estrogen drugs like progesterone and gonadotropin-releasing hormone agonists cause endometrial hyperplasia to reoccur (1,8). Medroxyprogesterone acetate is typically first line therapy for non-atypical endometrial

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hyperplasia but, these drugs have some complications. Various reports have shown some side effects such as adverse cardiovascular effects, increasing the load of lipids and lipoproteins, overweight, and mood changes due to consumption of progesterone (7). Treatment with gonadotropin-releasing hormone agonist results in osteoporosis and vasomotor effects (9-11).

Among other drugs that have been recently discussed for hyperplasia treatment, are aromatase inhibitors like letrozole and anastrozole that inhibit the aromatization of endogen into estrogen. Letrozole is a triazole derivative that is potent, reversible, competitive, nonsteroidal aromatase inhibitor. Letrozole cannot reduce the number of estrogen receptors. It can inhibit estrogen biosynthesis by 97% to 99%, resulting in estrogen concentrations below the level detected by most sensitive immunoassays. They are completely absorbed after oral administration and have a mean terminal half life of approximately 45 hours, clearance is mainly hepatic. This drug is useful in advanced breast cancer treatment as an adjuvant therapy. More recently, this medicine was used as a stimulant for women with child-bearing problem (7). In many studies, its complications are lower than other applied drugs for medical treatment of hyperplasia (8,12).

The aim of this study is to obtain medication for the treatment of endometrial hyperplasia with fewer side effects. Then we compared 2 applied medicines for hyperplasia treatment (medroxyprogesterone and letrozole) in patients with endometrial hyperplasia who were referred to the Abolfazle Health Clinic.

Material and Methods

This research is a randomized clinical trial (Trial Registration: irct.ir, Identifier: IRCT201510244339N12), conducted using a table of random numbers, after obtaining approval from the ethics committee and informed consent of participants.

At first, a vaginal ultrasound (Honda, 2100, Japan) was done by an experienced gynecologist on patients with abnormal bleeding, who were referred to Abolfazle clinic in Bushehr at the beginning of 2011 till late 2014. Endometrial thickness was estimated between 2 wide pints in the area of hyperechogenic in a vertical cut of the sagittal axis of the uterus. Inclusion criteria in the study consist of reproductive age women, lack of pregnancy and existence of simple endometrial hyperplasia in the pathology report.

The exclusion criteria in this research include non-reproductive ages, pregnancy, and existence of complex hyperplasia with atypia in pathology report, liver disease, existence of fibroids in uterus and existence of cyst in the ovaries.

When the endometrial thickness was more 12 mm, the curettage surgery was performed in the operating room for the referent patient, and the obtained sample was analyzed in the hospital's laboratory by 2 pathologists; therefore, patients with simple hyperplasia were studied in this research. After performing the curettage surgery and simple endometrial hyperplasia approval, at first, the level of blood estradiol was measured during the second and third day of menstruation, and then the patients were classified into two 40-person groups, based on the table of random numbers in Excel program. The first group was given a 5 mg medroxyprogesterone acetate tablet (Hormone Company, Iran). On the 16th day of menstruation, every night, 2 tablets were given 14 nights in each month for 3 months, and the second group was given 2.5 mg letrozole tablet (Hormone Company, Iran) continuously for 3 months. At the end of each month, the patients were visited regarding their menstruation condition and side effects, and all the data were recorded in the questionnaire. At the end of the third and sixth months, vaginal ultrasound was performed again for the patients, in order to analyze the endometrial thickness, and the blood's estradiol was measured again. In addition, endometrial biopsy was done, and pathology's report was followed.

Statistical Analyses

Statistical analysis was performed by the Statistical Package for Social Science (SPSS) version 11.5 for Windows (SPSS Inc., Chicago, IL, USA). The data was analyzed by student's t test, chi-squared test and t test for linear trend and proportions were compared. A P value of < 0.05 was considered to be statistically significant.

Results

In 2 case-study groups, 80 patients enrolled (40 patients in letrozole group and 40 patients in medroxyprogesterone group). There were no significant differences in the base variables. Age average in the group treated with medroxyprogesterone (group A) and the other group treated with letrozole (group B) was 36.15 ± 4.55 years and 37.15 ± 6.96 years, respectively ($P = 0.449$), and the difference was not significant. The body mass index (BMI) for groups A and B was 27.01± 4.97 kg/m^2 and 25.43 ±4.81 kg/m^2, respectively ($P = 0.104$). Thus, it indicates that there was no significant difference between the 2 groups. The level of estradiol in groups A and B before treatment was 52.6 ± 23.88 pg/mL and 62.98 ± 36.56 pg/mL ($P = 0.139$) which was similar in the 2 groups. Moreover, endometrial thickness in groups A and B was 15.60 ± 3.34 and 14.61 ± 3.83 mm, respectively ($P = 0.222$), and this difference was not statistically significant (Table 1).

In the letrozole-received group, the level of endometrial thickness before the treatment was 14.61 ± 3.83 mm and it reached 10.72 ± 3.65 mm after treatment. Moreover, this amount in medroxyprogesterone group was 15.60 ± 3.34 mm and it was 11.55 ± 5.78 mm after treatment. The difference between these 2 groups from the endometrial thickness reduction viewpoint is significant ($P < 0.0001$). The level of estradiol in serum in the letrozole group was 62.98 ± 36.56 pg/mL before treatment, and it reached 29.67 ± 23.69 pg/mL after treatment ($P = 0.0001$). This decline was significant, and in medroxyprogesterone group, it was 52.6 ± 23.88 pg/mL before treatment and 32.10 ± 17.30 pg/mL after treatment ($P = 0.0001$); thus, this difference is significant. Reduction percentage of the level of estradiol in

Table 1. Demographic of Patients in 2 Groups

Variable	Group A Mean ± SD	Group B Mean ± SD	*P*
Age (y)	36.15±4.55	37.15±6.96	0.449[a]
BMI (kg/m^2)	27.01±4.97	25.43±4.81	0.152[a]
Estradiol level before treatment (pg/mL)	52.6±23.88	62.98±36.56	0.139[b]
Endometrial thickness (mm)	15.60±3.34	14.61±3.83	0.222[a]

[a] Independent *t* test; [b] Mann-Whitney test.

Table 2. Comparison Between Endometrial Thickness and Estradiol Level Before and After Treatment in 2 Groups

Variable	Group A	Group B	*P*
Estradiol level after treatment (pg/mL)	32.10±17.30	29.67±23.69	0.602[a]
Endometrial thickness after treatment (mm)	11.55±5.78	10.72±3.65	0.445[b]

[a] Mann-Whitney test; [b] Independent *t* test.

serum in the medroxyprogesterone and letrozole groups is 37% and 42%, respectively ($P = 0.602$), and the difference is not significant (Tables 2 and 3). There was not any significant correlation between endometrial thickness and serum level of estradiol in both groups after intervention ($P > 0.05$).

In terms of comparing the menstrual status between the 2 groups and different stages of treatment, about 80%-90% of the patients had normal menstruation in the letrozole group and 65%-70% had normal menstruation in the medroxyprogesterone group. There was no significant difference between these 2 groups from the menstrual status standpoint between 2, 3 and 6 months after treatment. However, this difference was significant between before and after the treatment in each group, since all patients had hyper menorrhea (Table 4).

Discussion

The present study shows that there was no difference between endometrial thickness reduction after treatment with letrozole and medroxyprogesterone in childbearing-age women and hyperplasia without atypia, and their menstrual status was better than before the treatment.

Moreover, the study indicates reduction of serum estradiol level in the group given letrozole. This is not significantly more than reduction of serum estradiol level in the group which received medroxyprogesterone acetate.

This research shows that letrozole can be used to treat patients with simple hyperplasia, and they cannot undergo treatment with medroxyprogesterone, if they are sensitive to it and produce complications (like mood changes, and vascular and metabolic changes). In overweight patients with high level of estrogen (due to the storage of estrogen in adipose tissue) and in women who are in the late childbearing ages, there is the risk of other cancers like breast cancer. Therefore, they can use aromatase inhibitor as a complementary therapy, and it is also used for patients who have estrogen-secreting ovarian tumor.

A research was conducted by EL-Shamy et al on women with simple hyperplasia without atypia in which 2 groups were given letrozole and medroxyprogesterone, and at the end of the research, they mentioned that there was no significant and clear difference among the resistant, progressive and hyperplasia groups. Endometrial thickness was significantly reduced in patients who received letrozole as compared to those who received progesterone (1).

There was no significant difference between the present study and this research in the 2 groups, with regards to the endometrial thickness, and unlike this study, the present research showed that consuming letrozole and progesterone resulted in a decrease in endometrial thickness. However, similar to this study, the use of letrozole has significantly decreased the level of estradiol in serum as compared to progesterone. In a research conducted in 2012, the effect of progesterone and letrozole on endometrial thickness atrophy was equal in simple endometrial hyperplasia (1).

According to a research carried out by Baruah et al, endometrial thickness was analyzed regarding the comparison of letrozole and clomiphene citrate, and resistance and pulsate indexes were measured in spiral arteries of the

Table 3. Level of Decline in Estradiol and Endometrial Thickness After Treatment in 2 Groups

Group Treatment	Decline in Estradiol Level After Treatment		Decline in Endometrial Thickness After Treatment	
	Mean ± SD	*P* Value *	Mean ± SD	*P* Value[a]
A	20.49±16.04	<0.0001	4.05±6.64	<0.0001
B	33.31±16.04	<0.0001	3.89±4.55	<0.0001

[a] Independent *t* test.

Table 4. Menstruation in 2 Groups After Treatment

Duration of Treatment	Group A		Group B		*P* Value[a]
	Normal No. (%)	Hypermenorrhea No. (%)	Normal No. (%)	Hypermenorrhea No. (%)	
Two months after treatment	28 (70)	12 (30)	32 (80)	8 (20)	0.439
Three months after treatment	27(67.5)	13 (32.5)	34 (85)	6 (15)	0.115
Six months after treatment	28(70)	12 (30)	32 (80)	8 (20)	0.439

[a] Chi square test.

uterus by Doppler ultrasound, and it indicated that there was less vascular resistance; therefore, it affects endometrial thickness more and better than clomiphene citrate (13). The difference between our study and this research is that the compared group in this research is clomiphene, although at the end of the research, the endometrial thickness decreased like in our study.

Barker et al conducted a study on sixteen women, having a BMI of 34.5 in the post-menopausal period, and they had endometrial carcinoma and simple hyperplasia; therefore, they were treated with letrozole. As a result, the patients' endometrial thickness was decreased, but there was no response and inference for the four patients with metastatic disease (14).

This study differs from our research in which the average amount of BMI for this research patients was 34.5 and it indicates that these patients are overweight as compared to the our study with an average BMI = 28±4 in medroxyprogesterone group and BMI = 25±4 in letrozole group. However, as the number of people present in each group of BMI was low, this relationship could not be determined. This study was done on post-menopausal women, whereas our study was on women of reproductive-age, and the duration of treatment in this study was 36 months; in addition, endometrial thickness was decreased to about 81.7% (14.7 to 2.7 mm). The endometrial thickness in our study decreased from 14.6 to 10.7 mm. In a research performed by Li et al in 2008, letrozole was prescribed for 5 women with in childbearing age, which had endometrial hyperplasia. At the end of the research, reduction of serum estradiol level and recovery from hyperplasia was observed (8). Also in this research, both reduction of serum estradiol and reduction of endometrial thickness were observed after a 3-month treatment (15).

A study was done in which letrozole was prescribed for ten post-menopausal women with endometrial cancer. Generally, in the first stage, about fourteen days before surgery, the final result confirmed positive clinical change of letrozole (16).

In this study, the case-study group consisted of post-menopausal women, and the duration of treatment with letrozole was short. However, a positive effect was recorded in this study. All these studies show that the duration of treatment with letrozole affects the level of endometrial thickness reduction. The aromatase inhibitor (letrozole and anastrozole) inhibits the aromatization of endogen into estrogen peripherally (7,17).

There was no significant relationship between the 2 groups during 2, 3 and 6 months after the beginning of treatment in terms of the level of menstruation, but there was a significant difference before and after treatment.

Although the level of estradiol in serum was significantly reduced, there was no significant relationship between the 2 groups from the level of endometrial thickness reduction standpoint, and both had a rather equal decrease in the amount of thickness. One the important criteria in IVF cycle are endometrial thickness (18-23).

Conclusion

This study shows that letrozole can be used to treat patients with simple hyperplasia, who cannot undergo treatment with medroxyprogesterone or are sensitive towards this drug by producing some complications (like mood changes, vascular and metabolic changes).

Ethical Issues

Institutional Review Board of Bushehr University of Medical Sciences approved the study.

Conflict of Interests

The authors have no conflict of interest in this study.

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