



Effect of Letrozole on Endometrial Histology in Patients with Disordered Proliferative Endometrium and Simple Hyperplasia

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Article History:

Received 14 October 2013
Accepted 7 January 2014
Revised 25 December 2013
Available online 7 January 2014

Keywords:

Disorder Proliferative Endometrium
Hyperplasia
Letrozole
Megestrol Acetat

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Abstract

Objectives: This is a preliminary study investigating the efficacy of aromatase inhibitor letrozol on endometrial histology in patients with disordered proliferative endometrium or simple hyperplasia.

Materials and Methods: In a randomized clinical trial, 92 patients with abnormal uterine bleeding who had disordered proliferative endometrium or simple hyperplasia in endometrial biopsy, were randomized into case and control groups. patients received 2.5 mg of letrozole daily in case group (n=46) and 40 mg of megestrol acetate daily in control group (n=46) for 3 months. Endometrial biopsy was performed 3 to 4 weeks after completion of therapy to assess response.

Results: After intervention in letrozole group, response to treatment was seen in 93% cases (including endometrial atrophy in 58.7% cases and weakly proliferative endometrium in 34.78% cases) and in megestrol group response to treatment was seen in 85% cases (including endometrial atrophy in 41.3% cases and weakly proliferative endometrium in 43.47% cases). The difference between two groups was not statistically significant (P=0.31).

Conclusion: The results of this study show that pre and post menopausal women with disordered proliferative endometrium or simple hyperplasia can be successfully treated with letrozole alone. However, due to the lack of significant difference between the two groups, further studies with larger sample size is recommended for better clearance of the topic.

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Introduction:

Endometrial carcinoma is the most common malignancy of the female genital system. In recent years, certain factors are increasing awareness of endometrial cancer and emphasis on its diagnosis and treatment (1).availability of easily applied diagnostic tools and better understanding of endometrial premalignant lesions led to an increase in the number of women diagnosed endometrial cancer (2). This malignancy is a disease that occurs primarily in post menopausal period, and its prevalence increases with aging. The role of estrogen in the development of most endometrial cancers is established. Any factor increasing unopposed exposure of estrogen enhances the risk of endometrial cancer (3). From the pathogenesis perspective, there are two different types of endometrial cancer. Estrogen-dependent and non- estrogen dependent. Estrogen-dependent disease is responsible for 75-85% of cases which occurs in younger peri menopausal women (4). The tumors in these women begin as endometrial hyperplasia and develop to carcinomas. Endometrial hyperplasia reflects a spectrum of biological and morphological changes in endometrial glands and stroma which is variable from the resonance of physiological condition to carcinoma in situ (5,6).

In menopause, both estrogen and progesterone cease being produced by the ovaries under the gonadotropin stimulation, in contrast, androgen production is increased by the ovaries (7). The increased androgens are converted into estrogens by the enzyme aromatase which is mainly sited in the adipposed tissue. The result is a persistent endogenous production of estrogens causing an unopposed proliferative effect on the endometrium, which often leads to endometrial hyperplasia. for the reason that endometrial hyperplasia has been considered as an intermediate step in the estrogen driven pathogenesis of type 1 endometrial cancer (8,9). On the other hand, higher aromatase levels have been reported in hyperplastic than in normal endometrium (10). Currently, continuous treatment with

megestrol acetate is effective in removing proliferative disorders and endometrial hyperplasia without atypia, and but is less effective in cases with atypia (11,12). Several reports have emphasized the possible unfavorable vascular effects of progestins (13) and treatment by progesterone can also result in weight gain and mood changes(14).in recent years, several clinical trials on the use of letrozole in the treatment of endometrial hyperplasia has been done, which showed the need for further assessment of the effectiveness of this method.

Material & Methods:

In a randomized clinical trial (RCT), 92 patients with abnormal uterine bleeding with disordered proliferative endometrium or simple hyperplasia, were studied in two case and control groups (Group A and B respectively, each n = 46).The study was conducted in Alzahra Hospital, Tabriz University of Medical Sciences from February 2011 to April 2013. This study was approved by the ethics committee of Tabriz University of Medical Sciences, also it has been registered as a clinical trial N2 2012092310901 in IRCT site. The sampling was done randomly, using Rand List software. For this purpose, two errors, type I , 0/05, type II 50%,and the difference of 15% were considered.

Patients received 2.5 mg of letrozole daily in case group (n=46) and 40 mg of megestrol acetate daily in control group (n=46) for 3 months. Endometrial biopsy was performed 3 to 4 weeks after completion of therapy and endometrial sample was studied by two pathologists and the results of the pre and post treatment were compared by a gynecologic oncologist.

The exclusion criterias were allergy to letrozole, severely impaired hepatic function, uncontrolled hypertension and thromboembolism.

The results have been reported as Mean \pm SD, frequencies and percentages. SPSS™ 16 was used for statistical analysis. Student T-test and Fisher's Exact Test were used for quantitative variables and Chi-square was used for qualitative variables. In all studied

cases, the results having $P < 0.05$ were considered statistically significant.

Results:

Two groups were matched for demographic features (see table 1). Mean age of the patients in the group receiving letrozole was 49.23 ± 8.56 years and in the group receiving megestrol was 51.34 ± 10.06 years ($p = 0.170$). The mean age of the studied patients was 50.29 ± 9.35 years. The average number of pregnancies in the group receiving letrozole was 5.21 ± 2.91 and the group receiving megestrol was 5.06 ± 2.96 ($p = 0.643$). The average age of menarche in patients receiving letrozole was 11.50 ± 1.41 years and it was 11.65 ± 1.64 years in the group receiving megestrol ($p = 0.170$). In the group receiving letrozole, 22 patients (47.8 %) were post menopause and 24 patients (52.2%) were not menopause, in the group receiving megestrol 18 patients (39%) were not menopause and 28 cases (61%) were post menopause ($p = 0.148$).

In the group receiving letrozole, the menopausal age was 47.63 ± 1.94 years and it was 49.64 ± 3.04 in the group receiving megestrol, the age of menopause was not different between the two groups ($p = 0.061$). In Letrozole-treated group, 28 patients (60%) had a history of using oral contraceptive drugs (OCP) and 8 patients (18%) had a history of infertility treatment. In megestrol-treated group, 26 patients (56%) had the history of using oral contraceptive drugs (OCP) and 8 patients (18%) had a history of infertility treatment. In Letrozole-treated group, the side effects were as follows: headache in 6 patients (13%), insomnia in 5 patients (10.9 %) and flushing in 3 patients (6/5%) and no side effect was reported in 32 patients (69.6%). The side effects in the group receiving megestrol were: change in libido in 5 patients (10.9 %), increase in weight in 7 patients (15.2 %) and irregular bleeding in 8 patients (17.4 %), but no side effect was seen in 26 patients (56/5%).

Before treatment with letrozole group, endometrial histology was disordered proliferative endometrium in 39 patients (84%) and simple hyperplasia in 7 patients (16%). In megestrol group, endometrial histology was disordered proliferative

endometrium in 36 patients (78%), and simple hyperplasia in 10 patients (22%) ($p = 0.296$).

After intervention in letrozole group, response to treatment was seen in 93% cases (including endometrial atrophy in 58.7% cases and weakly proliferative endometrium in 34.78% cases), but 3 patients (6.5%) had no response to treatment (2 patient had simple hyperplasia and 1 patient progresses to complex hyperplasia) and in megestrol group response to treatment was seen in 85% cases (including endometrial atrophy in 41.3% cases and weakly proliferative endometrium in 43.47% cases) but 7 patients (15.21%) had no response to treatment (6 patient had simple hyperplasia and 1 patient progresses to complex hyperplasia). The difference between two groups was not statistically significant ($P = 0.31$) (see table 2).

Discussion:

The results of this study show that pre and post menopausal women with disordered proliferative endometrium or simple hyperplasia can be successfully treated with letrozole alone. Although, despite higher response rate to treatment in letrozole group, the difference between the two groups was not statistically significant.

Some trials have examined the use of letrozole in endometrial hyperplasia. In a study conducted by Crawford *et al.* the sustained effect of aromatase inhibitors on endometrial histology in 8 patients with endometrial hyperplasia (EH), 4 patients with localized endometrium adenocarcinoma (localized EA), and 4 patients with metastatic adenocarcinoma of the endometrium were examined. The results showed decrease in mean endometrial thickness both in women with EH and those with localized EA. aromatase inhibitors treatment was observed to have no effect on disease progression in women with metastatic EA (15).

In a study conducted at the University of Peking, China, letrozole was effective in the treatment of hyperplasia in 5 premenopausal women with irregular bleeding. In this study, letrozole was used with the dose of 2.5mg daily (16). In another

study at the Aristotle University in Greece, the effect of anastrozole (aromatase inhibitors) for treating endometrial hyperplasia in 11 obese post menopausal women were studied and endometrial hyperplasia was removed in all cases and 2 patients had atrophic endometrium (17). Brestein and Maximove have mentioned high success for aromatase inhibitors drugs, such as letrozole. Based on the findings these studies, letrozole could reduce endometrial thickness in patients with endometrial hyperplasia and in abnormal bleeding cases, it could stop the bleeding(18). Bernett and Colleagues also found that the combination of progesteron and anastrozole might be more successful than progesterin alone for the conservative management of well differentiated endometrial cancers in obese premenopausal women(19).Stefania and Hemendra reported a case of 58-year-old with recurrent endometrial carcinoma that was resistance to chemotherapy that was treated successfully with the aromatase inhibitore anastrozole(20).

Among cases and literature review of electronic resources ,no article was seen on comparing letrozole and megestrol in treatment of endometrial hyperplasia. Based on the results of our study, the use of letrozole in patients with disordered proliferative endometrium or simple hyperplasia had led to regression of endometrial proliferative disorders in 43 patients (93% of cases), On the contrary, in megestrol group, regression of endometrial proliferative disorders was seen in 39 patients (85% of cases). Also in the group receiving letrozole , the endometrial atrophy rate was 58.7% and it was 41.3% in megestrol group. And side effects in the group treated with letrozole was less than the group treated with megestrol.

Conclusion :

Based on our findings, we can conclude that the use of letrozole could be useful in the treatment of endometrial hyperplasia. In this study that compared the effects of two drugs of letrozole and megestrol in the treatment of endometrial hyperplasia and disordered proliferative endometrium, the response to the treatment in patients receiving letrozole and megestrol were 93%

and 85% respectively. Despite high response rate to treatment in letrozole group, the difference between the two groups was not statistically significant. Regarding to the lack of significant differences between the two groups, further studies with more number of cases is recommended for better clearance of the topic.

Conflicts of interest:

The authors declare no conflict of interest in this study

Acknowledgments:

We would like to thank authorities of Tabriz University of Medical Sciences for the scientific and ethical approval and financial support of this research. This study has been done as a thesis for specialty degree of Azadeh Azadi in Women's Reproductive Health Research Center Tabriz University of Medical Sciences. (proposal ID: 912, IRCT No: IRCT2012092310901N2).

Table 1. Demographic features

Patient Group	Mean Age	Age of Menarche	Number of Postmenopausal women (%)	Age of menopause	Number of pregnancy
letrozole Group (n=46)	49.23±8.56	11.5±1.41	22(47.8)	47.63±1.9 4	5.21±2.91
megestrol Group (n=46)	51.34±10.0 6	11.65±1.6 4	28(61)	49.64±3.0 4	5.06±2.96

Table2. Endometrial Histology after treatment

Patient Group	Weakly proliferative Endometrium (%)	Atrophic Endometrium (%)	Simple Hyperplasia (%)	Complex Hyperplasia (%)
letrozole Group (n=46)	16(34.78)	27(58.7)	2(4.3)	1(2.1)
megestrol Group (n=46)	20(43.47)	19(41.3)	6(13)	1(2.1)

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