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The Effect of Letrozole and Metformin on Endometrial Histology in Patients With Disordered Proliferative Endometrium

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Abstract

Objectives: This study intended to explore whether letrozole and metformin can change endometrial histology in the patients diagnosed with disordered proliferative endometrium.

Materials and Methods: In a pre- and post-interventional study, 31 patients with abnormal uterine bleeding (AUB) were participated to receive 5 mg letrozole and 500 mg metformin daily for 3 months after pathology report of disordered proliferative endometrium. The effect of this combination therapy on endometrial histology was evaluated through comparing the endometrial histology results before and after the intervention.

Results: After treatment with letrozole and metformin, 77.4% of patients showed significant response to therapy in the form of inactive and atrophic endometrium ($P < 0.001$). The clinical response to treatment was observed in 18 (58.1%) women as complete relief from bleeding and decreased hemorrhage in 6 (19.4%) women.

Conclusions: Based on the results of this study, letrozole and metformin can be successfully used for treatment of disordered proliferative endometrium. Hence, the effects of these medications deserve to be noticed for careful treatment of the patients with AUB.

Keywords: Letrozole, Metformin, Disordered proliferative endometrium, Abnormal uterine bleeding

Introduction

Abnormal uterine bleeding (AUB) is an extremely common gynecology complaint. AUB is the indication for two-thirds of hysterectomies and nearly 25% of gynecologic operations. An ovulatory cycle is common at 2 ends of reproductive period and usually is presented as proliferative endometrium. A chronic ovulation with hyper-estrogenic state increases the risk of endometrial hyperplasia or carcinoma (1). Letrozole as an aromatase inhibitor decreases the circulating estrogen level and can be effective in the treatment of peri-menopausal bleedings due to proliferative endometrial disorders (2-10). Letrozole reversibly binds to the aromatase-cytochrome P450 heme component and as a consequence, deters conversion of testosterone and androstenedione (Δ4A) into estrone and 17β-estradiol (E2), respectively. On the other hand, patients may become resistant to letrozole through complicated pathways; this problem may be resolved by using a combination therapy (11). Metformin, which is generally used in the treatment of type 2 diabetes, has low toxicity and is considered a relatively safe medicine with known pharmacokinetics. Additionally, the anticancer properties of metformin have been indicated in several studies (12,13). The major pathways explaining the anti-cancer role of metformin include: 1) activation of adenosine monophosphate kinase (AMPK) that causes inhibition of mTOR signaling pathways followed by suppression of cellular proliferation, 2) reduction of the circulating concentrations of insulin and insulin-like growth factor (IGF) leading to down-regulation of the IGF-receptor signaling pathways, which result in decrement in growth promotion and mitogenesis (14-19). Recently, a phase II trial showed that everolimus, an mTOR inhibitor, in combination with letrozole could be a more effective therapeutic strategy than mere letrozole (20). The results strongly offered that combination of metformin and letrozole may have some effects on postmenopausal uterine malignancies. The purpose of this study was to examine the histological changes of endometrium after using letrozole and metformin for treatment of the patients with disordered proliferative endometrium.

Materials and Methods

This longitudinal study was carried out at Alzahra hospital, Tabriz University of Medical Sciences from July 2013 to January 2015. Thirty-one women with premenopausal uterine bleedings who underwent endometrial biopsy and diagnosed with disordered proliferative endometrium after taking written informed consent were included in the

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study. The participants received letrozole (2.5 mg b.i.d.) and metformin (500 mg daily) for 3 months. Patients with sensitivity to letrozole and metformin, severe liver or renal dysfunction, uncontrolled hypertension or history of thromboembolism were excluded from the study. Endometrial biopsy was repeated at the end of treatment and endometrial samples were studied by a pathologist who was blind to the subjects. Data were analyzed using SPSS 17.0 and Student's *t* test, Fisher exact test, and chi-square. The *P* value < 0.05 was considered significant.

Results

A total of 31 patients met the inclusion criteria and were included in the study. The mean age of the patients was 48.39 ± 3.9 years, (age range: 40-55 years). The significant characteristics of patients are summarized in Table 1. The average duration of AUB was 1.64 ± 0.5 (age range: 1-3 years).

Nineteen patients (61.3%) had taken hormone therapy in a form of either oral contraceptive (OCP) or progesterone previously. The mean age of menarche was 12.59± 1.27 years. The average numbers for gravida, parity, and abortion were 3.6, 3.3, and 0.36, respectively. Most of the patients were illiterate (25.8%) or had primary education (51.6%) and lived in urban areas (64.5%). Only 29.1% of patients had background medical conditions such as hypertension, diabetes mellitus, or ovarian polycystic disease.

The significant histological changes in endometrium as an inactive or atrophic endometrium were observed in 24 (77.4%) patients after treatment with letrozole and metformin (*P* < 0.001).

The treatment was clinically effective in 18 (58.1%) cases as completely stopped bleeding and in 6 (19.4%) patients as decreased amount of bleeding. As shown in Table 2, the treatment was not effective in 7 (22.6%) cases with a background of proliferative endometrium (*P*< 0.001).

The minor side effects in the patients receiving letrozole and metformin were: headache in 4 patients (12.5%), flushing in 6 patients (19.3%), and weight loss in 7 patients (22.5%), but no major side effects were seen.

Table 1. The Demographic Features of the Patients

Characteristics	Range	Mean (± SD)
Age (y)	40-55	48.39(±3.9)
Menarche age (y)	10-16	12.59 (±1.2)
AUB (y)	1-3	1.64 (±0.5)
Gravida (N)	1-7	3.6
Parity (N)	0-7	3.2
Abortion (N)	0-1	0.38
Educational levels	**No. (%)**	
Illiterate	8 (25.8)	
Elementary	16 (51.6)	
Diploma	7 (22.5)	
Background disease	**No. (%)**	
No	22 (70.9)	
Yes:	9 (29.1)	
HTN	5	
DM	3	
PCO	1	
Previous hormone therapy	**No. (%)**	
OCP	9 (29)	
progesterone	10 (32.3)	

Abbreviations: OCP, oral contraceptive pills; HTN, hypertension; DM, diabetes mellitus; PCO, polycystic ovary.

Table 2. Histologic and Clinical Response to Treatment With Letrozole + Metformin

Response to treatment	No. (%)	*P* value
Histologic response		0.001
Inactive/atrophic endometrium	24 (77.4)	
Proliferative endometrium	7 (22.6)	
Clinical response		0.001
Relief of bleeding	18 (58.1)	
Decreased bleeding	6 (19.4)	
Continued bleeding	7 (22.6)	

Discussion

Many of epidemiologic and experimental studies have reported the role of unopposed estrogen in development of endometrial benign, premalignant, and malignant lesions and AUBs (21-25). Disordered proliferative endometrium could be the first level of the estrogen-driven endometrial changes. Aromatase inhibitors, such as letrozole, may show a therapeutic effect at this stage by suppressing the peripheral conversion of androgens to estrogens. A study conducted by Gharabaghi et al compared the effect of letrozole with megestrol in the treatment of AUB due to disordered proliferative endometrium or simple hyperplasia. They concluded both medications similarly affected the selected patients. The histological response to letrozole was reported as atrophic endometrium in 58.7% and weakly proliferative endometrium in 34.78% of cases. Other studies carried out by Barker et al, Li et al, and Berstein et al on the cases of endometrial hyperplasia or adenocarcinoma revealed that letrozole was successful in decreasing endometrial thickness and stopping bleeding (27-29). Moreover, the same results were reported from using anastrozole, another aromatase inhibitor, for treatment of hyperplastic endometrium (30).

On the other hand, Tabrizi et al studied the antiestrogenic effect of metformin in the patients with AUB diagnosed with disordered proliferative or simple hyperplastic endometrium and showed good response in 95.5% of cases who took 1000 mg metformin daily for 3 months versus 61.9% response in megestrol group (31).

Several studies confirmed that metformin could be used as an effective drug in the treatment of disordered proliferative endometrium (32,33). In the current study, to assess the effect of these two drugs together, for the first time, we aimed to evaluate the effect of letrozole and metformin on endometrial histology in the patients with disordered proliferative endometrium. Based on

our results, significant clinical and histologic responses to the treatment with letrozole and metformin were observed in 77.5% and 77.4% of cases, respectively. This study demonstrated that combination of letrozole and metformin could be used as a new and effective therapy in the patients with disordered proliferative endometrium.

Conclusions

Treatment of disordered proliferative endometrium with letrozole and metformin is effective in most of the patients; however, the success of this therapeutic strategy should be reassessed in a randomized clinical trial.

Conflict of Interests

All authors declare that they have no competing interests.

Ethical Issues

The research proposal was approved by the Ethics Committee of Tabriz University of Medical Sciences (5/4/2963) and registered at the Iranian Registry of Clinical Trials (www.irct.ir, No. IRCT2012092310901N2).

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