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Effect of Aromatase Inhibitors in the Treatment of Endometrial Hyperplasia in Post Menopausal Women

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Abstract:

Objective: *To explore the effect of aromatase inhibitors in the treatment of endometrial hyperplasia in post menopausal women.*

Materials and Methods: *This observational longitudinal study was undertaken in 21 postmenopausal women diagnosed as having endometrial hyperplasia in a private clinic in Dhaka between July, 2009 to January 2014. Initially hyperplasia was diagnosed by thickened endometrium by ultrasound and confirmed by histopathologic examination of fractional curretage. Among the patients, 7 had complex hyperplasia without atypia; 14 had simple hyperplasia without atypia. All the patients were treated with letrozole 2.5 mg per day for 12 months and were monitored by transvaginal ultrasonogram every 3 months, subsequently followed up by history and transvaginal ultrasonogram 6 monthly for another 12 months. Main outcome measure was reduction of endometrial thickness. Informed written consent was obtained before enrollment in the study.*

Results: *Mean endometrial thickness decreased by 81.66% following 12 months of treatment and the endometrial thickness was not increased in next 12 months follow up period. All patients were symptom free during this treatment.*

Conclusion: *The results of this study indicate that treatment of endometrial hyperplasia with aromatase inhibitors can reduce endometrial thickness. So, aromatase inhibitors deserve attention for the conservative treatment of endometrial hyperplasia.*

Keywords: *aromatase inhibitor, endometrial hyperplasia, postmenopausal women.*

Introduction:

Endometrial hyperplasia is thought to be caused by prolonged, unopposed oestrogenic stimulation of endometrium[1]. Postmenopausal women who are overweight are at increased risk of both endometrial cancer and endometrial hyperplasia and this risk may be due to increased aromatase activity in obese patients[2]. Endometrial hyperplasia is an oestrogen driven disease. Antioestrogen treatment with progestins or oestrogen deprivation with gonadotrophin – realeasing hormone agonists have been shown to reverse endometrial hyperplasia[3]. However, several reports have been emphasized the potentially unfavorable vascular effects of progestins as well as elevated lipid and lipoprotein levels[4]. Progestin treatment can also result in weight gain and mood changes[5]. Treatment with gonadotrophin realeasing hormone agonists has been found to have the same vasomotor and osteoporotic effects as hypoestrogenic treatment[6]. Aromatase converts androgen into oestrogens; this conversion occur in extra glandular sites such as adipose tissue.Aromatase inhibitors (AIs) [e. g. anastrozole and letrozole] reduce the level of circulating oestrogen[7,8]. It is currently administered to post-menopausal women with advanced breast cancer to reduce estrogen production due to peripheral

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aromatization of androgen. 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[9,10]. Aromatase levels have been reported in hyperplastic than in normal endometrium . Furthermore, the expression of aromatase is even higher in atypical hyperplastic endometrium[11]. The intratumoral biosynthesis of estrogen is important in endometrial cancer development and progression[12,13]. Though dilatation and curettage is a common method to treat endometrial hyperplasia, the actual effect is not so ideal, the reason mainly lies in that the curettage only shaves the thickened endometrium, it does not eliminate the actual cause of endometrial hyperplasia (unopposed oestrogenic stimulation of endometrium)[1,14]. In recent years, several clinical trials on the use of letrozole in the treatment of endometrial hyperplasia has been done. This present study was undertaken to investigate the effect of aromatase inhibitors in the treatment of endometrial hyperplasia in post menopausal women.

Material and method:

This longitudinal study was performed among twenty one postmenopausal women presented in a private clinic in Dhaka for postmenopausal bleeding or thick endometrium on ultrasound between July, 2009 to January, 2014.The postmenopausal women diagnosed histologically as having endometrial hyperplasia by fractional curettage (that included whole – wall circumferential curettage) due to postmenopausal bleeding or thick endometrium on ultrasound. Twenty one cases were taken for this study by purposive sampling.Inclusion criteria was histologically confirmed endometrial hyperplasia without atypia. Exclusion criteria was patients with endometrial hyperplasia with atypia, patients getting any type of hormonal treatment like progesterone or history of taking that within 6 months ;patients with co-morbidities like Tuberculosis, history of taking any immunosuppresive drug and patients with known case of osteoporosis.Outcome variable was endometrial thickness.Independent variables were BMI, blood pressure, pre- treatment blood sugar level. The postmenopausal women diagnosed histologically as having endometrial hyperplasia by fractional curettage due to postmenopausal bleeding or thick endometrium on ultrasound who fulfilled the inclusion criteria were included in this study. An informed written consent was taken before enrollment. Particulars of the patients and the findings of general, abdominal, per vaginal per- rectal examination and pre-treatment blood sugar level was recorded. The histopathology report after fractional curettage and the initial endometrial thickness obtained from USG were recorded. All the patients were treated with letrozole 2.5 mg per day for 12 months. Patients were followed up upto 24 months by interview and performing transvaginal ultrasound at 3 monthly intervals for first 12 months and then 6 monthly for next 12 months. Data were collected with special attention to endometrial thickness and to any side-effects.

Responses to treatment in all women was based on endometrial thickness measured by performing transvaginal ultrasound at 3,6,9,12,18 and 24 months.Data was analyzed using SPSS version 17 (SPSS Incorporation, Chigo,IL,USA). Student's 't' test was done for test of significance. A value <0.05 was considered as significant.

Results:

A total of 21 postmenopausal women met the criteria and were included in the study. The mean age of the patients were 61.81 years ± 6.6 (range 51-72 years). Mean BMI of the patients calculated was 34.25kg/m^2± 4.35 (range 28.4 kg/m^2-40.50 kg/m^2) [Table I]. Histopathology report revealed that 66.66% of patients had simple endometrial hyperplasia followed by complex endometrial hyperplasia without atypia in 23.8% of patients, and 9.5% patients had complex atypical hyperplasia [Table II]. Among 21 patients, 14.28% of patients had diabetes mellitus, 19.04% of patients had been suffering from hypertension and both diabetes mellitus and hypertension was present in 66.66% of patients [TableIII]. The mean endometrial thickness at '0' month (pre-treatment) was 11.45mm ± 1.67 (range 9mm-14.7mm). At 3 months, the mean thickness was 6.57mm ± 1.27 (range 4.3mm-8.7mm). At 6 months it was 4.8 mm± 0.08 (range 4.2mm-5.3mm), at 9 months the mean endometrial thickness was 4.2 mm± 0.98 (range 3.4 mm-4.9mm) and at 12 months the mean endometrial thickness was 3.05 mm± 0.55 (range 2.1mm-4mm). There was significant reduction of endometrial thickness after 12 months of treatment ($p<0.05$). [TableIV]. During treatment with aromatase inhibitors (AI s), mean endometrial thickness decreased progressively by 81.66% from 14.7 mm at the start of treatment to 2.1 m1m following

Table-I

Demographic chacteristics of the patients(n=21)

Parameter	Mean ± SD	Range
Age (yrs)	61.81 ± 6.60	51-72
BMI (M^2/Kg)	34.25 ± 4.35	28.40-40.50

Table-II

Type of Endometrial Hyperplasia (n=21)

Type of Endometrial Hyperplasia	No. (n=21)	Percentage
Simple hyperplasia without atypia	14	66.67%
Complex hyperplasia without atypia	7	33.33%

Table-III

Co- morbidities among the patients (n=21)

Diseases	No(n=21)	Percentage
Diabetes Mellitus	3	14.28%
Hypertension	4	19.04%
Diabetes Mellitus & Hypertension	14	66.66%

Table-IV

Endometrial thickness before and after treatment with Letrozole

Months	Endometrial thickness (mm) before treatment		Endometrial Thickness (mm) after treatment		Significance
	Range	Mean±SD	Range	Mean±SD	
3 months	9-14.7	11.45±1.67	4.3-8.7	6.57±1.27	p = 0.042
6 months	9-14.7	11.45±1.67	4.2-5.3	4.8±1.08	p = 0.035
9 months	9-14.7	11.45±1.67	3.1-4.9	4.2±0.98	p = 0.028
12 months	9-14.7	11.45±1.67	2.1-4	3.05±0.55	p = 0.008

12 months of treatment. The endometrial thickness did not increase in next 12 months of follow up period and all the patients were symptom free during this treatment.

Discussion:

The treatment for endometrial hyperplasia in postmenopausal women usually involves hysterectomy because this is the potentially curative treatment for endometrial hyperplasia. However, co-morbidity precludes this in some patients and non-surgical treatments have been explored, usually systemic progestogens. For endometrial hyperplasia, progestogen- releasing intrauterine devices have proven superior to oral administration with long- term benefit being shown[13,15].

Endometrial thickness greater than 5 mm on ultrasound in postmenopausal women is regarded as the cut off point for further investigation. Using this as a surrogate endpoint for this treatment, the results of this study has shown that, for patients with endometrial hyperplasia this threshold was attained within 12 months of treatment.

Following the first 3 months of treatment, decrease in mean endometrial thickness was seen in postmenopausal women with endometrial hyperplasia. At the end of the 6 months, 9 months and 12 months of treatment, a further decrease in mean endometrial thickness was seen in those patients. The finding of this study is further supported by studies conducted by the Oncology Department of Airedale General Hospital, UK. They used aromatase inhibitors in the treatment of endometrial hyperplasia and endometrial carcinoma and their conclusion was that treatment with anastrozole or letrozole can reduce endometrial thickness in patients with endometrial hyperplasia and in patients with localized endometrial adenocarcinoma but have no effect on disease progression in women with metastatic endometrial adenocarcinoma[16]. Overall decrease in mean endometrial thickness following 12 months was 11.3mm(66.3% of original thickness) in those with localized endometrial adenocarcinoma and 7.5mm (51.1% of original thickness) in those with endometrial hyperplasia[16]. In the UK study, the treatment was continued for another 2 years that revealed that following the second 12 –month period, the mean endometrial thickness of patients with endometrial hyperplasia continued to decrease and fell by a further 3.4 mm; in patients with localized endometrial adenocarcinoma, endometrial thickness had leveled off and a mean reduction of just 0.03mm was seen at the 24 months point. Between 24 and 36 months of treatment endometrial thickness fell by a further 1.1mm in patients with endometrial hyperplasia compared with 0.1mm in patients with localized endometrial adenocarcinoma[16].

The result of this present study also support the studies in the use of aromatase inhibitors in the treatment of breast cancer, where tamoxifen- related proliferation of the endometrium is seen to be reversed and where the incidence of new endometrial pathology on this treatment is reported to be low[17].

Another study conducted by the Centre for Reproductive medicine, Peking University in China showed the efficacy of letrozole in the treatment of

five premenopausal women presenting for infertility were diagnosed as having endometrial hyperplasia with or wirhout atypia. At the end of treatment with letrozole 2.5mg daily for 3 months repeat curettage of the endometrium revealed no evidence of endometrial hyperplasia or atypia in any of the patients[18].

Agorastos et al. found that anastrozole reduced mean endometrial thickness, ultrasonically measured, from 11.2mm before treatment to 4.1mm at 6 months and 2.7mm at 12 months of treatment in a group of 11 patients with a mean body mass index(BMI) of 36kg/m^2 [12].

Burnett and colleagues also found that the combination of progestin and anastrozole might be more successful than progestin alone for the conservative management of well- differentiated endometrial cancer in obese premenopausal women[19].

A recent study in Iran showed that pre and postmenopausal women with disordered proliferative endometrium or simple hyperplasia can be successfully treated with letrozole alone[20].

In the present study follow up was performed by transvaginal ultrasound only and repeat curettage was not performed as sonographic ultrasound finding of endometrial thickness correlate with the endometrial histopathlogy[21].

A study done by Nasri et al regarding the role of vaginal scan in measurement of endometrial hyperplasia in postmenopausal women showed that there is a correlation of ultrasound findings and endometrial histopathology. In 63% of patients endometrium was atrophic and the ultrasound endometrial thickness was 5 mm or less. In 31% of patients, the endometrial histology was abnormal and ultrasound endometrium was greater than 5mm and they suggested that an endometrial thickness of 5 mm is an appropriate cut-off level for conservative management of patients with postmenopausal bleeding[20].

The results of this present study has shown that postmenopausal women with endometrial hyperplasia 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 postmenopausal women.

In this study the follow-up time is short and need to be extended. More experience with a larger sample size and randomized control trial is required before aromatase inhibitors can be accepted as safe and effective for the medical management of endometrial hyperplasia.

Conclusion:

Treatment of endometrial hyperplasia without atypia with letrozole can reduce endometrial thickness. This result indicates that aromatase inhibitors deserve attention for the conservative treatment of endometrial hyperplasia in postmenopausal women sepecially when surgery is not feasible. However, the success of this kind of treatment should be evaluated after a long term randomized trial.

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