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Original Research

Effect of prolonged use of Aromatase inhibitor Letrozole on increasing the risk of cardiovascular accidents in pre-menopausal women

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ABSTRACT

Introduction: Uterine myomas are very common benign tumours of the uterus. The patients may not be willing or may not be fit for surgical procedures. Medical management is done in a few cases. The perimenopausal age group is high risk for cardiovascular accidents. Hence, the side effects of the medical management should be considered.

Material and Methods: The study was done in 30 perimenopausal patients with uterine myomas. 2.5 mg of Letrozole (Aromatase Inhibitor) was given for 3 months. The hormonal profile and lipid profile was done to know about the risk of increasing cardiovascular accidents in these patients.

Results: Letrozole when used for 3 months did not change the hormonal profile and lipid profile of the patients.

Keywords: Aromatase Inhibitor, Letrozole, Cardiovascular accidents

INTRODUCTION

Uterine myomas, the most common solid benign tumours originating mainly from smooth muscles of uterus, occur in 20 - 40% women in their reproductive years.[1] Their growth has shown to be associated with exposure to circulating estrogen and hence a growth spurt is exhibited during pregnancy and in premenopausal years, secondary to more anovulatory cycles.[2] The estrogen receptors in myomas bind 20% more estradiol (E2) per milligram to cytoplasmic protein than the normal adjoining myometrium.[1] The tumours also maintain high sensitivity to estrogen during the estrogen dominated follicular phase of the menstural cycle, unlike normal myometrium.[3]A lot of treatment modalities are available for uterine myomas. One such medical treatment in patients who are not the candidates for surgical procedures arearomatase inhibitors. Letrozole, a nonsteroidal aromatase inhibitor commonly used in anovulatory infertility in the follicular phase has been suggested to have potential therapeutic role in treatment of leiomyoma and endometriosis.[4] Aromatase, a member of cytochrome p 450 super family, is a microsomal enzyme that catalyses the conversion of androgens to estrogen. Letrozole is a potent (97-99% potency) and highly specific, third generation aromatase inhibitor that was approved initially for use in post menopausal women with breast cancer to block estrogen production.[5]In leiomyoma of the uterus, both aromatase and 17 beta hydroxysteroid dehydrogenase (17 beta-HSD) type1 enzymes are over expressed in comparison with normal myometrium.[6] This suggests that leiomyoma cells convert circulating androstenedione into estrone (via aromatase) and then into the active form of estrogen, estradiol.[6] Inhibition of aromatase enzyme by letrozole would block this conversion and hence result in hypoestrogenic environment. As the growth of leiomyoma is positively correlated to circulating estrogen levels, the hypoestrogenic mileau would be inhibitory to myoma growth.[7]Anastrozol, inhibitor of aromatase, is a highly selective, third-generation nonsteroid substance. The aromatase inhibitor used in the treatment of uterine leiomyoma offers a series of advantages over the analogues of GnRH. Primarily, the differential inhibition of estrogen synthesis in the leiomyoma and ovary can reduce the volume of the leiomyoma without the systemic side effects observed when using GnRH analogues (phenomenon of ‘‘flareup’’ and menopausal symptoms in general). Hence, complete suppression of estrogen production in the leiomyoma and partial suppression in the ovary is obtained.[7] This is similar to what occurs in patients using analogues of GnRH that merely cause partial reduction of estrogen levels but display reduction of uterine volume. Anastrozole is given in the dose of 1mg per day and letrozole 2.5mg per day for12 weeks.It acts by inhibiting or inactivating aromatase, the enzyme which catalyses the synthesis of oestrogens from androgenic substances such as androstenedione. In contrast to ovariectomy, treatment with letrozole doesnot lead to an increase in serum FSH. Letrozole selectively inhibits gonadal steroidogenesis but has no significant effect on adrenal mineralocorticoid or glucocorticoid synthesis. Letrozole inhibits the aromatase enzyme by competitively binding to the heme of the cytochrome P450 subunit of the enzyme, resulting in a reduction of estrogen biosynthesis in all tissues. Leiomyoma cells and subcutaneous fat cells express aromatase, and are therefore able

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to synthesize oestrogen.[8] This observation may explain a possible therapeutic role for aromatase inhibitors in the treatment of symptomatic fibroids in premenopausal and menopausal women. As the age increases, perimenopausal patients have increased risk of cardiovascular accidents.

Methods

The proposed prospective study was carried out on 30 symptomatic premenopausal women between 35 - 50 years of age with menstural or pressure symptoms on bowel or urinary system and having either a single intra uterine myoma of size 4 cms or more or one myoma of size of 4 cms or more and additional one or more myomata each of size 2cms or less attending the Department of Obstetrics and Gynaecology, Pt. B.D. Sharma, PGIMS, Rohtak. Patients with impaired renal functions, pregnancy, oral administration of any type of estrogen and progesterone more recently than onemonth, previous hormonal or surgical treatment for leiomyomata or history of previous deep vein thrombosis, cardiovascular disease were excluded from the study. All selected subjects were given tablet Letrozole 2.5 mg per day for 12 weeks, regardless of the day of the menstrual period.While on therapy, the patients were called for follow up visits after 4 weeks,8 weeks and 12 weeks. On each visit patient had undergone history taking for improvement or deterioration of symptoms, compliance and documentation of any adverse effects was evaluated, clinical examination for myoma and uterine size, serum FSH, LH, estradiol (E2) testosterone levels and lipid profile and pelvic ultrasonography to note any alteration in uterine myoma size, volume and echopattern was done.Data collected was subjected to statistical analysis and standard tests for significance. Paired t test and ANOVA was applied.

Results

The present study was a prospectivestudy conducted on 30 patients attending the Out Patient Department of Obstetrics and Gynaecology, PGIMS, Rohtak. The patients were selected based on the inclusion and exclusion criteria mentioned under material and methods. Tablet Letrozole 2.5 mg once a day was given to the enrolled women for 12 weeks. The patients were called for monthly follow up during the therapy to ensure regimen adherence, study the hormonal profile and reporting of any adverse effects of the drug.The majority of the patients were 45 years of age, however the mean age was 45.06±0.54 years.Serum levels of LH, FSH, estradiol (E2), progesterone and testosterone, lipid profile during treatment with letrozole have been compared in tables I, II, III, IV, V and VI.

1. Serum LH (mIU/ml)
2.

Table : I showing serum LH levels over 12 weeks period

S. LH (mI U/ml)	D0	4 weeks	8 weeks	12weeks
<5	6	8	9	10
5.1-20	17	14	13	12
20.1-35	3	5	5	4
35.1-50	2	1	2	2
50.1-65	2	2	1	2
>65	0	0	0	0
Mean ±2SD	15.32±5.6	15.18±5.4	15.59±5.2	15.22±5.6

It is evident from table I that 23 patients (76.66%) had serum LH levels below 20 mIU/ml, though all women in the study had levels in the normal range. At the end of 12 weeks, 22 patients (73.33%) had serum LH below 20 mIU/ml.By using repeated measure ANOVA, p value was found to be 0.84 which is >0.05, i.e LH levels had not significantly changed during treatment with letrozole.

3. Serum FSH (mIU/ml)
4.

Table: II Table showing serum FSH levels over 12 weeks period

S.FSH (mIU/ml)	D0	4 weeks	8 weeks	12weeks
<10	9	12	12	11
10.1-20	11	7	7	8
20.1-30	3	2	3	3
30.1-40	1	3	2	2
40.1-50	1	2	2	1
50.1-60	1	1	0	1
>60	4	3	4	4
Mean ±2SD	25.72±9.2	24.46±8.6	25.54±8.8	24.55±8.8

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It is evident from table II that 23 women (76.66%) at enrolment and 22 women (73.33%) at the end of 12 weeks had serum FSH values lower than 30 mIU/ml, the mean values being 25.72± 9.2 mIU/ml and 24.46± 8.6 mIU/ml respectively. The p value was found to be 0.077, thus indicating an insignificant change in serum levels of FSH over the 12 weeks period.

5. Serum estradiol (E2) (pg/ml)

Table III
Table showing serum estradiol levels

S.E2 (pg/ml)	D0	4 weeks	8 weeks	12weeks
<20	1	3	1	1
20.1-200	18	18	20	19
200.1-400	8	8	8	9
400.1-600	3	1	1	1
>600	0	0	0	0
Mean±2SD	175.04±52	162.91±45.6	159.72±45.8	163.97±43.4

26 women (86.66%) out of 30 at enrolment and 28 women (93.33%) at the end of 12weeks had serum estradiol values between 20.1 to 400 pg/ml, and the mean values were 175.04±52 pg/ml and 163.97±43.4 pg/ml respectively. There was no significant difference in change of serum estradiol (p value 0.288) prior to initiation and during therapy with letrozole.

6. Serum progesterone (ng/ml)

Table: IV
Table showing serum progesterone levels over 12 weeks period

S. Progesterone (ng/ml)	D0	4 weeks	8 weeks	12 weeks
<1	17	15	16	16
1-5	12	13	12	13
>5	1	2	2	1
Mean±2 SD	1.47±0.52	1.64±0.58	1.66±0.64	1.54±0.56

It is evident from table IV, 17 patients (56.66%) at enrolment, and l6 patients (53.33%) after 12 weeks of treatment had serum progesterone less than 1 ng/ml. Mean values were 1.47±0.52 and 1.54±0.56 respectively.p value was found to be 0.229, i.e the change in progesterone levels during treatment is not significant (p>0.05).

7. Serum testosterone (ng/ml)

Table V
Table showing serum testosterone levels over 12 weeks period

S. Testosterone (ng/ml)	D0	4 weeks	8 weeks	12 weeks
<10	0	0	0	0
10.1-25	6	8	9	6
25.1-40	14	11	11	14
40.1-55	6	9	6	6
55.1-70	4	2	4	4
>70	0	0	0	0
Mean±SD	36.53±14.67	33.84±13.73	34.91±13.33	35.53±13.11

Table V shows that 20 patients (66.66%) at enrolment and 20 patients (66.66%) at 12 weeks had serum testosterone levels between 10.1 to 40 ng/ml, with mean values of 36.53±14.67 ng/ml and 35.53±13.11 ng/ml respectively. All the patients in the study had serum testosterone value within the normal range for an adult female (0-70 ng/ml). The p value was found to be 0.3, i.e the change in testosterone levels during treatment was not significant.The lipid profile assessment was done at enrolment and after 12 weeks.

Table VI
Lipid profile of the patients

Lipid profile	D0	12 weeks
Deranged	0	0
Not deranged	30	30

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The lipid profile of all the patients included in the study was found to be within normal limits both at enrolment and at 12 weeks. Table XXI shows the lipid profile done at enrolment and at 12 weeks of therapy. Hence, letrozole was not found to alter the lipid profile in the patients.

Discussion

Since aromatase inhibitors catalyzes the conversion of androgens to estrogen, the aromatase inhibitors would logically appear to have a role in the management of uterine leiomyoma. A few aromatase inhibitors like letrozole, fadrozole and anastrozole have been tried for the same.Letrozole is an aromatase enzyme inhibitor and it has no or minimal role in changing the endocrinal levels in the subjects. The present study also has been shown to have the same result.The change in serum LH was found to be not significant with p value of 0.84 ($p > 0.05$). There is no flaring up of LH when on treatment with letrozole as the drug does not have any hypoestrogenic effect. Similar results were found by Parsenehad et al with Letrozole 2.5 mg for 12 weeks with p value of 0.660 (insignificant).[9]The change in serum FSH was found to be insignificant with p value of 0.77. Hilario et al and Parsanezhad et al have concluded in their study that aromatase inhibitors did not change the levels of FSH after 12 weeks of treatment.[9,10] Similar results have been obtained in the present study. Since the action of aromatase inhibitors is primarily localized in the myomas which have a higher expression of aromatase enzyme, the drug does not cause hypoestrogenism and hence has no significant effect on serum FSH.In our study, the change in serum Estradiol levels was insignificant. In premenopausal women, ovaries are the major site of estrogen production while in postmenopausal women, estrogen is chiefly produced from extragonadal sites. Aromatase inhibitors inhibit the conversion of androgens to estrogen. The ovaries of premenopausal women are able to overcome this blockade, thereby preventing any hypo estrogenic side effects in them.Shozu et al gave Fadrozole to a53 years old perimenopausal patient and found a decrease in serum levels of LH, FSH and Estradiol, however the finding was unexplainable.[4]Letrozole also did not change the values of serum Progesterone.Aromatase inhibitors have target specific action, hence there is no significant change in testosterone levels. The study conducted by Parsanezhad et al and Hilario et al also gave same results.[9,10]

Conclusions

It may be concluded from the present study that aromatase inhibitor, Letrozole has a beneficial role in symptomatic premenopausal women with fibroids. The drug is fairly safe, with no major adverse effect and no participant discontinuing the treatment midway through therapy period. The risk of developing cardiovascular accidents is also not increased with its use. The prolonged use of Letrozole for 12 weeks did not alter the hormonal profile and lipid profile of the subjects. Thus, Letrozole is a promising option for management of premenopausal patients with fibroids. However, the need for larger trials cannot be understated.

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