Aromastase Inhibitor Therapy For Symptomatic Uterine Leimyomata In Premenopausal Women

Abstract

Objective: To examine the effect of letrozole on symptomatic leiomyomata.

Patients and Methods: In a prospective, intervention study, forty six premenopausal women with fifty two leiomyomata were invited to take 5 mg letrozole daily for 3 treatment cycles of 28 days each. Leiomyoma, uterine and ovarian volumes, endometrial thickness, gonadotrophins, and the scores of menstrual pictograms and Uterine Fibroid Symptom and Health Related Quality of Life (USFS – HRQoL) were recorded at the start and conclusion of this study.

Results: Letrozole resulted in 53.29% mean reduction in original leiomyomata volumes (P < 0.01) without significant reduction in myoma free uterine tissue. Estradiol levels dropped significantly from baseline levels (64.32 ± 16.77 (mean ± SD) to (40.83 ± 12.032) pg/ml (p<0.001) at the end of this study.

Conclusion: Adding to its significant shrinkage of leiomyomata, letrozole improved leiomyoma related symptomology, quality of life and menstrual pattern significantly.

Introduction

Uterine leiomyomata are the most common benign tumors in the female reproductive tract with an incidence ranging from 5.4 % to 77% (1), and are responsible for 33% of hysterectomies performed in the United States (2).

Ovarian steroids particularly estrogen are important factors for fibroid growth. This fact is supported by the increased incidence of symptoms from these tumors among women in their 30s and 40s (3), the rare occurrence of myomata before puberty, their regression after menopause (4) and the higher expression of estrogen and progesterone receptors in uterine myomas compared to the normal myometrium (5), (6). Besides, deprivation of ovarian estrogen as seen during gonadotropin releasing hormone – agonist (GnRH a) therapy causes leiomyomata to shrink significantly (7).

Symptomatic leiomyomata treatment is mainly surgical; however, numerous hormonal agents have been used for their management (8). Aromatase, a member of cytochrome P450 superfamily is a microsomal enzyme that catalyzes the conversion of androstenedione and testosterone by hydroxylation to estrone and estradiol respectively (9). Bulun and coworkers (10) in 1994 reported that aromatase mRNA concentrations are 1.5-2.5 times higher in leiomyomas than in the surrounding myometrium, which illustrates their ability to synthesize estrogen in situ and allows their independence from ovarian estrogen (11). Letrozole is a potent and highly specific nonsteroidal aromatase inhibitor that was approved initially for use in postmenopausal women with breast cancer to block estrogen production (12). This study was done to examine the efficacy of letrozole on symptomatic uterine leiomyomata in premenopausal women regarding reduction of volumes and control of symptoms.

Patients and methods

This prospective study was held in Obstetrics and Gynecology Department of Zagazig university hospital between July 2007 and April 2009. Forty six Egyptian women attending the outpatient clinic were enrolled for this study. All of the study participants were symptomatic premenopausal women with ovulatory menstrual cycles ranging from 26-30 days, they were presented with no more than two leiomyomata of at least 35 mm in diameter. Women with neoplastic, metabolic endocrine, renal, liver, hematologic and infectious disease, history of acute recurrent or past thromboembolic disease, body mass index (BMI) > 30 kg/m², history of osteopenia or osteoporosis or presence of hypothyroid or calcified leiomyomata detected at ultrasonography were excluded from this trial. Endometrial abnormalities as ovarian cysts detected by transvaginal ultrasound were among exclusion criteria. Women who smoke and women trying to become pregnant; requiring or requesting immediate surgical treatment were not included, as well. Patients were required to have a washout period of at least 3 months for hormonal medication before screening. Women fulfilling inclusion criteria were prescribed letrozole (Femara, Novartis Pharm AG, Basle Switzerland) 5 mg i.e 2 tables daily for 12 weeks. All women signed an informed consent after explaining aim and potential risks of treatment, and all of them agreed to use barrier contraception during study period.
Sonographic assessment

The examination included an initial 2-dimensional ultrasound assessment of the uterus using 7.5 MHz endovaginal probe and a 2.5 MHz abdominal probe of a Voluson Expert 730 TM GE Medical Systems, Zipf, Austria). Number and size of leiomyomas, uterine size, and ovarian size were assessed at the start of the study and at the end of first and third treatment cycles. The position of the fibroids within the uterus was not specifically recorded further to previous evidence that symptoms of heavy menstrual bleeding do not appear to correlate with fibroid location (13). All dimension measurements (D1, D2, D3) were done twice and the mean was recorded (where D1=length, D2=anteroposterior diameter and D3=transverse diameter). Leiomyoma and uterine volumes were calculated by using the ellipsoid formula: \( V = \frac{4}{3} \pi \times \frac{D1 \times D2 \times D3}{2} \times 0.5 \) (14), using the integrated machine software. An arithmetic mean of the sizes was used in the presence of two leiomyomas (15). All women were asked to describe their menstrual patterns and keep a menstrual calendar over the three cycles of treatment.

Menstrual pictogram (MP)

The severity of uterine bleeding was carefully recorded by each woman using the menstrual pictogram (MP) introduced by Higham et al (16) and modified and validated by Wyatt et al (17), the score is calculated in milliliters and is equivalent to the actual volume of blood lost.

UFS-Qol

Before treatment cycles and at the end of the study, patients completed the Uterine Fibroid Symptom and Health Related Quality of life HRQL questionnaire (UFS-Qol) (18), with HRQL and its 6 subscales of concern, effect on activities, energy mood, control, self-consciousness, sexual function score and the score of symptom severity.

Laboratory study

Laboratory analyses included hematological, serum follicle stimulating hormone FSH, luteinizing hormone (LH) and estradiol measurements at trial entry and at the end of the first and third treatment cycles. FSH and LH were measured with immunoradiometric assay (IRMA) using commercial kits \(^{125}\) I-FSH and \(^{125}\) I-LH IRMA Kits. Institute of Isotopes Company Ltd, Budapest, Hungary). Estradiol levels were obtained with radioimmunoassay (RIA) using commercial kits Ultra-Sensitive, Estradiol RIA DSL 4000, (Diagnostic Systems laboratories, Webster TX).

Outcome measures

The change in leiomyoma volume was set as the primary outcome measure in this study. A minimal required sample size of 33 leiomyomata was calculated to achieve 85% power at a alpha level of 1% in detecting a 50% change in the volume of leiomyomata with an anticipated volume of 160 ml and a standard deviation of 120 ml. The selected secondary outcome measures in this trial were changes in the uterine volume, difference between uterine and leiomyomata volumes, endometrial thickness, hematocrit, gonadotropins, estradiol, menstrual pictograms and self-reported symptom and health related quality of life HRQL score. Adverse drug reactions were also secondary outcome measures among. Statistical analysis and sample size were done with SPSS 15.0 (SPSS Inc, Chicago, IL).

Results

Forty-six women with fifty-two leiomyomata were recruited for this study. Demographic characteristics of study population at the inception of this study are pointed out in table (1).

All women pulled through the study period despite the presence of side effects viz: follicular cysts (13 patients; 27.7%), hot flushes (10 patients; 21.3%), Dyspareunia (8 patients, 17%), vaginal dryness (6 patients, 13%), hair thinning (5 patients, 10.9%) and headache (4 patients, 8%). These side effects were not serious and were well tolerated by affected women. The mean volume of uterine leiomyomata decreased significantly by the end of first treatment cycle (P < 0.001) and again after the last 2 cycles (P < 0.05) (table 2).

Table (1): Demographic characteristics of study population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>37.3 ± 5.6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.6 ± 2.3</td>
</tr>
<tr>
<td>Parity (n)</td>
<td>2.68 ± 1.1</td>
</tr>
</tbody>
</table>

*Values are reported as mean ± standard deviation

At study conclusion letrozole resulted in a mean 53.29% reduction of the original leiomyoma volume mean reduction ± SD was 57.72 ml ± 49.813. No change in leiomyoma volume by end of treatment was noted in 4 patients. For women at 40 years of age or older, there was significant leiomyoma size reduction, the reduction was non-significant for women forty years of age or younger. Fig. (1).

Table (2): Variables studied at entry and throughout study period

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>First Cycle</th>
<th>Third Cycle</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine size (cm³)</td>
<td>298.82 ± 163.62</td>
<td>219.23 ± 98.75*</td>
<td>199.88 ± 78.55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Leiomyoma size (cm³)</td>
<td>105.49 ± 112.31</td>
<td>73.32 ± 72.16*</td>
<td>56.22 ± 61.04*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Δ Size *</td>
<td>159.31 ± 46.2</td>
<td>152.6 ± 41.3</td>
<td>146.9 ± 49.4</td>
<td>NS</td>
</tr>
<tr>
<td>Endometrial thickness (mm)</td>
<td>8.17 ± 4.21</td>
<td>8.02 ± 4.8</td>
<td>7.6 ± 3.8</td>
<td>NS</td>
</tr>
<tr>
<td>Ovarian size (cm)</td>
<td>9.71 ± 1.75</td>
<td>10.94 ± 9.34</td>
<td>19.63 ± 15.174</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Length of uterine bleeding(d)</td>
<td>4.9 ± 1.2</td>
<td>2.1 ± 2.6</td>
<td>1.7 ± 1.9</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Hematocrit %</td>
<td>33.41 ± 4.521</td>
<td>35.02 ± 2.632</td>
<td>37.14 ± 4.023</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FSH IU/L</td>
<td>7.31 ± 2.746</td>
<td>13.04 ± 10.131*</td>
<td>15.62 ± 118.92</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LH IU/L</td>
<td>6.22 ± 1.784</td>
<td>10.24 ± 10.042*</td>
<td>11.46 ± 11.173</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>E2 Pg/mL</td>
<td>64.32 ± 16.775</td>
<td>43.47 ± 10.412*</td>
<td>40.83 ± 12.032</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- Data are expressed as mean ± standard deviation.
- Δ Size: Difference between uterine size and leiomyoma size.
- Significantly different from previous result.
Fig (1):
Changes in leiomyoma volume mean ± standard deviation below and above age of 40 years

* P < 0.05 compared with previous volume.

Fig (2) Changes in leiomyoma volume (mean ± SD)

Concerning leiomyoma size, it was appeared that tumors > 50 mm in diameter showed significant reduction in size after the first (p < 0.01) and the last 2 cycles (p < 0.05) of letrozole therapy fig. (2). Reduction was not significant in small (50 mm or less) leiomyoma. Mean uterine size decreased significantly by the end of the trial (mean reduction ± SD; 96.83 ± 86.15 ml) p < 0.001. The mean reduction was 31.12% of the original volume unlike leiomyoma, there was no relation between age of 40 years or older and the decrease in uterine volume. Letrozole was not found to have a significant effect on the normal myometrium (the difference between uterine and myoma volumes) as presented in table (2). Mean ovarian volume increased significantly at the end of 3rd treatment cycle compared to the end of first one, mean increase ± SD; 9.89 ± 14.42 ml, the mean increase was 36.88% above initial ovarian volume. Hematocrit was significantly increased at termination of this study (p < 0.01).

The mean increase in hematocrit value was 13.67% of the mean at the beginning. No interaction between hematocrit and age > 40 years was present. Levels of gonadotrophins studied showed a significant elevation after the first 28 days of therapy, levels continued to rise over the remaining period however it was not significant.

*Statistically significant at <0.05 level compared to baseline.

Fig (3):

UPS-QoL questionnaire analysis of mean changes in total score and subscales from baseline to final visit for symptom severity, a lower score = lower severity, for other scales higher = better quality of life.

Alternatively, estriol (E2) levels plunged significantly at the end of the first 28 days of letrozole intake. Levels continued to fall but the decrease was not significant. Mean estradiol (E2) level decreased by 36.52% below levels at study entry. The briefings collected from patients demonstrated a significant decrease in the self-reported scores of symptom severity i.e. vaginal bleeding, pelvic pain pressure, fatigue (p < 0.001), however there was no change in urinary frequency. The menstrual pattern improved significantly and women with regular cycles increased from 21% at baseline to 67% at the end (p < 0.001). Besides, HRQoL scores and its 6 subscales showed significant improvement at final visit compared to the start of study fig. (3). At trial end, menstrual pictogram (MPs) calculated scores decreased significantly below those reported before treatment. Mean MP scores ± SD at baseline was 215.8 ± 107.6 ml and dropped to 59.3 ± 18.7 ml at final observation. Mean ± SD of difference = 126.5 ± 88.9 ml (p < 0.05)

Discussion

Letrozole (an aromatase inhibitor), treatment in this study was associated with a significant (53.29 %) reduction, of leiomyoma size in premenopausal women after a three cycle-treatment (p < 0.01). These results are in concordance with those of GnRHa used alone in five randomized controlled trials (RCTs) (19). However, the significant reduction in uterine size 35 – 65 % (20), and the significantly increased proportion of patients with amenorrhea after 3 months of GnRHa treatment compared to placebo (51 % with megestrol vs 8 % with placebo p < 0.05 ) (21), clouded their benefits. Conversely, letrozole treatment as magnified in this study was not associated with amenorrhea despite significant reduction in (MP) scores.

Add – back regimens to overcome hypoestrogenic effect of GnRHa and to permit extension of treatment have been tried using medroxyprogesterone acetate (22), tibolone, (23) estrogen
alone (24) combined with progesterin (25), or raloxifene (15).

Raloxifene has been used alone in high dose to inhibit the growth of leiomyomata in premenopausal women but growth of new leiomyomata has been observed even during low dose treatment (15). There is limited evidence that add-back therapy can reduce menopausal symptoms and/or loss of bone with GnRH. Results regarding uterine or leiomyoma size were inconsistent and even insignificant and it may be useful in older premenopausal women with lower background estradiol concentration (15). Ru 486 (mifepristone); a high progesterone receptor affinity antiestrogen was tried as well, but it appears to have unopposed estrogenic effect with high rate of endometrial hyperplasia (26).

In this study there was no change in endometrial thickness throughout and after 3 months of letrozole treatment. More recently a selective progesterone receptor modulator (SPRMs) Asoprisnil has been tested but the uterine and fibroid volumes were reduced in a dose dependent manner. The largest 25 mg dose reduced uterine volume by 36% but caused a reversible suppression of menstruation, and variable effects on ovulation (27). So far, no RCTs evaluated the levonorgestrel releasing intrauterine system in women with fibroids (28). Dopamine receptor agonists were recently shown to shrink myomas as an adjunct to surgical management (29). Rapid resumption of pretreatment uterine volume was remarkable with GnRH. The only drug known to have a "carry-over effect" in which the size of the uterus continues to decrease after treatment discontinuation is gestrmine, however, androgenic side effects viz. weight gain, seborrhea / acne are limitations to its use (30).

Whether the volume reduction observed with letrozole is sustained after treatment discontinuation or not needs to be evaluated. The same applies to anastrazole (another aromatase inhibitor). Nevertheless, previous studies (31), (32) pointed out that the half life of both letrozole and anastrazole is between 40 and 50 hours and within 4 weeks of stopping them little drug remains.

The non myoma uterine volume was significantly reduced in many studies addressing GnRHa effects on uterine size (33). This was not the case in this study where the difference in non myoma uterine volume from baseline to the end of trial was insignificant. Other studies employing letrozole (34), (35) or anastrazole (36), (37) agreed with findings of this study. This could be explained by the fact that levels of aromatase mRNA are 1.5 - 25 times higher in the leiomyoma than in surrounding myometrium (10). Shrinkage of myomas in postmenopausal women treated with aromatase inhibitors is a proof of the above - mentioned explanation since ovarian estrogen production in these women is nearly absent (38). The significant reduction of leiomyoma volume in women over 40 years was noted in this study and other studies using aromatase inhibitors (37) declares a remarkable effect on this age group.

In this study, the location of myomas was not specified because previous studies with (37) or without (13) aromatase inhibitors showed no effect of leiomyoma location on tumor volume reduction or menstruation. Estradiol levels decreased significantly p < 0.01 by the end of the first treatment cycle, the reduction continued till the end however it was not significant. Same results were replicated in previous studies (39) which pointed out the significant drop in estradiol levels in premenopausal women 4 to 5 weeks after the start of letrozole treatment.

It is conceivable that letrozole a competitive inhibitor of aromatase which is the rate limiting step in conversion of the androstenedione and testosterone to the estrone and estradiol respectively (9), so aromatase inhibitors inhibit both gonadal and ovarian estrogen production unlike the majority of medical therapies that impact ovarian estrogen production only. Indeed, aromatase inhibitors have been shown to suppress estrogen levels to 95% of their pretreatment values in postmenopausal women where estrogen production is derived from a non gonadal source (40). More recently Bedaiwy and co-workers (41) manifested that letrozole prevented the estrogen associated flare effect known to happen 1 day after the injection of GnRH in premenopausal women with endometriosis. Consequently, estrogen serum levels start to decline as early as the first day after aromatase inhibitors administration (42) indicating the superiority of aromatase inhibitors over GnRHa in medical treatment of leiomyomata. Using another potent aromatase inhibitor, anastrazole. Varella and colleagues could not detect any significant change in estradiol levels throughout their 3 (28 days) cycles of treatment (36).

Previous reports demonstrating that letrozole suppresses plasma estradiol and estrone sulphate more completely than anastrazole in postmenopausal women with breast cancer (43) could provide an explanation of this dichotomy. Besides, women in this study received 2 tablets 5 mg versus 2.5 mg/day in the previous (43) study, the anastrazole dose however was the same in both studies, so the increased estrogen suppression of letrozole may be dose dependent. Letrozole is known to be the most potent agent of the third - generation aromatase inhibitors in vitro (44). The answer to whether the greater estrogen suppression with letrozole is clinically relevant will have to await further trials.

Gonadotropins (FSH, LH) increased exponentially after treatment p < 0.01. Conversely earlier studies (39) reported their reduction 4-8 weeks after treatment using letrozole. Again using anastrazole Verasas et al (37) failed to find any change in gonadotropins. In this study, Follicular Cysts developed in 11 patients (23.9%).

Ovarian size increased remarkably for each treatment cycle p < 0.01, same was noted by Gurutes et al (34). These findings were expected as letrozole is used to induce ovulation (45). Oral contraceptive were not allowed in this study to get the probable almost benefit of estrogen suppression induced by letrozole. It is pertinent to mention that estrogen lowering drugs may promote osteoporosis or decrease bone mineral density (BMD), increasing the number of bone fractures in patients (46). Even though, further studies are required to confirm this. Earlier experimental studies (47), actually, recorded that letrozole did not affect BMD as well as recent clinical studies (34). Finally, significant improvement of quality of life and hematoctit values was noted in this study. Similarly improvement was reported in previous studies using other agents (20), (27).

In conclusion, this study is not blinded, controlled or randomized which is the stigma of studies devised to demonstrate effectiveness of medical therapies in uterine leiomyomata. This underscores the difficulty of making definitive conclusions above the safety of drugs manipulating hormones in premenopausal women with fibroids. High-quality RCTs are urgently needed for this common problem.

References