

A randomized, controlled clinical trial comparing the effects of aromatase inhibitor (letrozole) and gonadotropin-releasing hormone agonist (triptorelin) on uterine leiomyoma volume and hormonal status

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Objective: To examine and compare the efficacy and safety of GnRH agonist (GnRHa) vs. aromatase inhibitor in premenopausal women with leiomyomas.

Design: Multicenter, randomized, controlled clinical trial.

Setting: University hospitals.

Patient(s): A total of 70 subjects with a single uterine myoma measuring ≥ 5 cm. Subjects were randomized into two groups with use of a random table. They were treated with aromatase inhibitor (group A) or GnRHa (group B).

Intervention(s): Group A received letrozole (2.5 mg/d) for 12 weeks. Group B received triptorelin (3.75 mg/mo) for 12 weeks.

Main Outcome Measure(s): Measurement of myoma volume and E₂, FSH, LH, and T levels.

Result(s): Total myoma volume decreased by 45.6% in group A and 33.2% in group B. Reductions in myoma volume in the two groups were statistically significant. There was no significant change in hormonal milieu in group A. The serum level of hormones significantly decreased in group B by the 12th week of treatment.

Conclusion(s): Uterine myoma volume was successfully reduced by use of an aromatase inhibitor. Rapid onset of action and avoidance of initial gonadotropin flare with an aromatase inhibitor may be advantageous for short-term management of women with myomas of any size who are to be managed transiently and who wish to avoid surgical intervention, specifically women with unexplained infertility having uterine myoma. (*Fertil Steril*® 2010;93:192–8. ©2010 by American Society for Reproductive Medicine.)

Key Words: Uterus, myoma, medical therapy, aromatase inhibitor, GnRHa

Uterine leiomyomas are the most common benign tumors of the uterus (1). These tumors are estrogen (E) dependent, develop during the reproductive period, and are suppressed with menopause (2). Receptors for both E and P have been identified in leiomyomata (3). In addition to ovarian E, some investigators have shown that leiomyoma tissues are a source of E. Leiomyoma cells express an E synthetase as well as aromatase and convert circulating androgens to E (4–9). Estrogen secreted by leiomyomata tissue may reach a sufficient con-

centration within the local compartment to support its own growth, allowing independence from ovarian E (10).

Traditional treatments for myomas have been various types of surgical techniques. Hysterectomy has long been viewed as the definitive management of symptomatic uterine myomas (11, 12). Myomectomy by laparotomy, hysteroscopy, and laparoscopy are the principle mode of treatment for women with these tumors who wish to save their fertility (13, 14). Recently more conservative approaches such as myolysis, ultrasound thermoablation, uterine artery embolization, and uterine artery ligation have been introduced (15–18).

Medical management of uterine myomas is an approach that has been used recently and is attractive for many gynecologists because of its relative ease and lack of complications (pelvic organ adhesion) compared with surgery. Indications for therapy are similar to those for surgical removal of myoma and would focus on preserving fertility

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and/or the patient's desire to maintain her uterus. Medications used include androgens (19), antiprogestogens (mifepristone) (20), raloxifene (21, 22), and GnRH agonist (GnRHa) (23–28).

However, considering efficiency and safety issues, none of the above agents obtained adequate popularity except for GnRHa, which is used in anemic patients as an adjunct to surgery (29). Long-acting GnRHa induces amenorrhea and reduces uterine volume by reduction in ovarian hormone secretion. This treatment, however, is often associated with hypoestrogenic symptoms, including vasomotor instability, vaginal dryness, and significant bone loss, which preclude the long-term use of this compound (29, 30).

In vitro studies and clinical trials support the notion that the use of the aromatase inhibitor letrozole inhibits leiomyoma growth. In these studies the investigators reported that aromatase inhibitor significantly reduces myoma volume without any significant side effects after 8 weeks of treatment (31).

This clinical randomized trial is the first study that was conducted to examine and compare the efficacy and safety of GnRHa vs. aromatase inhibitor in premenopausal women with leiomyomas.

MATERIALS AND METHODS

Study Design

This was a prospective, randomized, multicenter, assessor-blind trial performed between February 2006 and April 2008 in the teaching hospitals affiliated with Shiraz University of Medical Sciences (Shiraz, Iran) and Diako Teaching Centre, Göttingen University (Bremen, Germany). A total of 70 subjects with a single uterine myoma measuring ≥ 5 cm were eligible to be included in the study. Women with myomas measuring ≥ 5 cm who had additional myoma(s) with diameter < 2 cm were also included. Subjects were randomized into two treatments groups using a random table. They were treated with aromatase inhibitor (group A) and long-acting GnRHa (triptorelin) (group B). Because, for technical reasons, GnRHa was supplied in vials and aromatase inhibitor in tablets, a double-blind study design was not feasible. Instead an assessor-blind design was chosen, whereby preparation and administration were performed by a person who did not take part in any decision concerning medication administration during the study.

The study was approved by the ethics committee of the university, and each subject provided written informed consent before participating in the study.

Subject Selection

Subject included in the study were [1] premenopausal women aged 18–42 years with a single intramural uterine myoma > 5 cm with abnormal uterine bleeding, unexplained infertility, pelvic pain, dysmenorrhea, and pressure effect, or [2] women with a myoma measuring ≥ 5 cm who had additional myoma(s) with diameter < 2 cm.

Excluded subjects included [1] women who had additional myoma(s) measuring ≥ 2 cm, [2] women with uterine myoma who were under treatment with any type of E or P more recently than 1 month and with hormonal implant more recently than 3 months, and [3] women with a history of major medical problem and/or previous medical or surgical treatment for leiomyomata. All women with myomas measuring 2–5 cm were also excluded.

Study Drugs and Study Procedures

Aromatase inhibitor (letrozole) was purchased locally in Iran and administered orally (2.5 mg/d), regardless of the day of menstrual period.

The GnRH agonist triptorelin (Diphereline; Ipsen Pharma, Paris, France) was purchased locally in Iran and was administered IM in a dose of 3.75 mg monthly, starting after complete pretreatment workup.

All subjects underwent baseline measurement, performed in the early follicular phase. An expert gynecologist performed all transvaginal ultrasound scans and analysis. Briefly, a D 4000 (Honda, Japan) ultrasound machine with a 5.5-MHz vaginal probe was used for scanning. After identification of the myoma, its volume was calculated with a stepwise planimetry method using an integrated software program. Measurements were performed at baseline and during treatment at weeks 2, 4, 6, and 12, and mean values were calculated.

Serum samples were obtained at baseline and at 2, 4, 6, 8, and 12 weeks after the start of treatment. Aliquots were stored at -20°C until being assayed. All hormones (FSH, LH, E_2 , and T) were assayed by RIA.

Statistical Analysis

Baseline data analysis for patients designated to either protocol was performed with the grouped Student's *t*-test to assess the effectiveness of randomization. The changes occurring in the independent variables (myoma and uterine sizes, hormonal changes) were assessed both within a given protocol group longitudinally over time and between protocol groups at the designated times of measurements. The findings of significant differences from baseline for measurements at 6 weeks to the final 12 weeks within groups were determined by a multivariate analysis of variance, using a test of repeated measures of individual subjects. Between-protocol differences were assessed by two-tailed grouped Student's *t*-testing of volume changes occurring over the designated time interval. Significance was defined as $P < .05$. Normal values of hormonal levels were defined as follows: FSH, 5–20 mIU/mL; LH, 5–20 mIU/mL; T, 0.2–2.8 nmol/mL; E_2 , 20–400 pg/mL.

RESULTS

Of the 70 women initially randomized, 60 complete the study: 33 (55%) received letrozole (2.5 mg) (group A), and 27 (45%) received triptorelin (3.6 mg/mo) (group B). Ten

TABLE 1

Baseline characteristic of subjects treated with letrozole (group A) or triptorelin (group B).

Characteristic	Group		P value
	A	B	
Ag (y)	30.94	31	.971
E ₂ (pg/mL)	66.448	67.793	.660
FSH (mIU/mL)	5.521	5.759	.283
LH (mIU/mL)	5.555	5.496	.830
T (nmol/mL)	1.221	1.206	.911
Myoma volume (cm ³)	108.18	95.29	.526

Note: Values are means.

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patients were withdrawn from the trial: two from the letrozole group and eight from the triptorelin group. None of these patients discontinued therapy because of an adverse event. The major reason for withdrawal was irregular follow-up visits. Sixty patients completed the study protocol, and the data analysis was performed on these 60. Overall there was no significant difference in patient baseline characteristics between the two groups (Table 1).

Myoma Volume

A pattern of reduction in myoma volume from baseline was noted in both groups between weeks 2 and 12 (Fig. 1). There was no statistically significant difference between the two groups in myoma volume at the end of the treatment period (week 12).

Total myoma volume is presented as the percentage change from baseline in Table 2. The total volume of myoma declined by 45.6% at week 12 in group A ($P=.00$). During the same period, myoma volume declined by 33.2% in group B ($P=.02$). Reduction in myoma volume at the end of the treatment protocol was similar in both groups ($P=.00$). Although not statistically significant, the total decline in myoma volume was greater and more rapid in group A.

Hot Flashes

No subject in group A developed hot flash, whereas 96.3% of patients in group B reported various degrees of hot flash; the difference was statistically significant ($P=.00$).

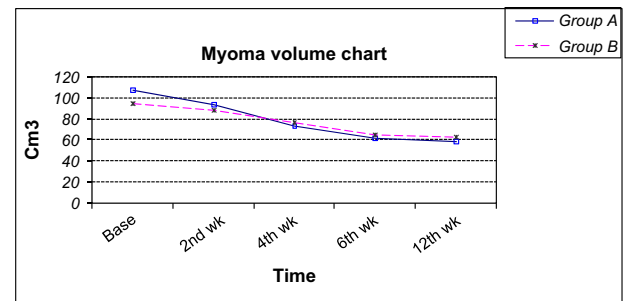
Hormonal Changes

To evaluate the effects of letrozole and triptorelin on hormonal milieu, serum levels of E₂, FSH, LH, and T were measured at baseline and 2, 4, 6, and 12 weeks after the start of treatment. Results of these measurements are shown in Table 3.

Serum E₂ concentrations rose during the first 2 weeks of treatment in group B, whereas this value showed a mild de-

FIGURE 1

Pattern of effects of letrozole (group A) and triptorelin (group B) on leiomyoma volume during 12 weeks of treatment. Leiomyoma volume was assessed at baseline and during treatment at weeks 2, 4, 6, and 12 by transvaginal ultrasound. Myoma volume declined significantly in the two groups ($P<.05$). There are no significant differences between the two groups in myoma decline.



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crease in group A ($P=.11$). Serum gonadotropin (FSH and LH) levels also declined in group A but increased from baseline to week 2 in group B; the changes were not significant. Thereafter, the mean LH, FSH, E₂, and T concentrations decreased dramatically at all treatment visits in group B, with the maximum effect at week 12. The difference was statistically significant compared with baseline ($P=.00$). There were no statistically significant changes in hormonal values at all visits in group A. The patterns of hormonal changes at various treatment visits in both groups are shown in Figures 2, 3, 4, and 5 for E₂, FSH, LH, and T, respectively.

Ovarian and Follicular Changes

No significant changes were noted in ovarian size and follicles. However, nonsignificant follicular growth was observed in group A.

DISCUSSION

This was the first prospective, randomized clinical trial comparing the effects of letrozole and long-acting GnRHa (triptorelin) on myoma volume and hormonal status. We designed our protocol on the basis of aromatase inhibitors' ability to create a local hypostrogenic state in uterine myoma. To simplify the randomization, we included symptomatic subjects with a single myoma measuring ≥ 5 cm. Women who had additional myomas with the size < 2 cm were treated, but the changes were not taken into account in statistical analysis.

Because treatment of asymptomatic myoma is not ethically allowed, we included symptomatic women with fibroids. However, because symptom changes were not part of our main outcome measures, the changes were not taken

TABLE 2

Total myoma volume as percentage change from baseline in patients treated with letrozole (group A) or triptorelin (group B).

Group	Myoma volume (cm ³)													
	Baseline	P	Wk 2	Decline (%)	P	Wk 4	Decline (%)	P	Wk 6	Decline (%)	P	Wk 12	Decline (%)	P
A	108.18		94.345	12.79	.044	73.885	31.7	.00	61.98	42.71	.00	58.86	45.6	.00
B	95.29	.526	88.607	7.02	.048	76.880	19.33	.057	65.47	31.3	.025	63.66	33.2	.02

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into account in our study. The only parameter that was measured was the size of myoma. The results of this randomized, assessor-blind study demonstrate the clinical potential of letrozole to reduce uterine leiomyoma volume.

Many studies have reported the potential usefulness of the hypoestrogenic state induced by GnRHa for treatment of leiomyoma (32, 33). A GnRHa downregulates the pituitary-ovarian-gonadal axis, leading to suppression of ovarian steroidogenesis. The mentioned agents reduce E levels to those occurring after menopause or after surgical oophorectomy (34), and their use in the treatment of myomas has been associated with fibroid shrinkage (32, 33). However, their use is associated with temporary induction of symptoms of the menopause.

In addition to ovarian E, recent works have reported the possible contribution of in situ E to leiomyoma growth, namely E synthesized in leiomyoma cells. Leiomyomas express E synthetase (aromatase P450) at a higher level than the surrounding myometrium and are able to synthesize Es (35, 36). Letrozole has been shown to inhibit leiomyoma growth in an in vitro study (37). Recently the aromatase inhibitor was examined and reported to reduce the size of myoma by 71% without side effects after 8 weeks of treatment (38).

In the present study we demonstrated an average reduction of 47.3% in myoma volume with the use of letrozole (2.5 mg/d) for 12 weeks, with no significant changes in serum E₂, T,

and gonadotropin levels. The result is in agreement with those of a previous study (38). Our data show a reduction in myoma volume without systemic hypoestrogenism in the letrozole group. This was probably due to the application of the small dose of letrozole (2.5 mg). There are some reports showing that the small dose of letrozole for the premenopausal period was insufficient for inhibiting production of E₂ in the ovary. The ovary is the main site for aromatase action (39, 40). Because the aromatase inhibitor does not cause systemic hypoestrogenism, it does not generate the side effects that were observed in the GnRHa group.

The side effects of GnRHa (hot flashes and E₂, T, and gonadotropins reduction) were significantly higher in group B. Although the myoma volume significantly declined from baseline in both groups (P=.00), group B showed a slower rate of volume reduction.

Shozu et al. (38) published a case report on aromatase inhibitor treatment. In addition to a 71% reduction in myoma volume, they found a significant reduction in E₂ and gonadotropins. They also observed full signs of a hypoestrogenic state in the case. As they stated, there is no satisfactory explanation for the hormonal changes and hypoestrogenic state. Incipient ovarian failure or menopause might be the cause of this phenomenon, unrelated to the effects of aromatase inhibitor.

Considering our data and the results of other publications, we conclude that the use of aromatase inhibitors has several advantages over GnRHa therapy; serum levels of E start to

TABLE 3

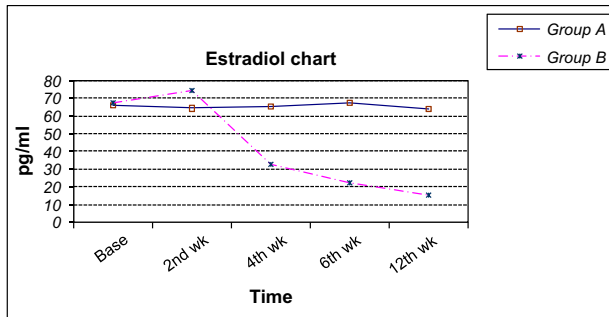
Hormonal levels at baseline and during treatment with letrozole (group A) and triptorelin (group B).

Hormone	Group	Baseline	P	Wk 2	P	Wk 4	P	Wk 6	P	Wk 12	P
E ₂ (pg/mL)	A	66.448	.660	67.736	.11	65.870	.00	67.503	.00	64.415	.00
	B	67.793		74.656		33.144		22.322		15.570	
FSH (mIU/mL)	A	5.521	.283	5.427	.003	5.342	.00	5.274	.00	5.236	.00
	B	5.579		6.848		3.233		2.189		1.737	
LH (mIU/mL)	A	5.555	.83	5.433	.12	5.40	.00	5.33	.00	5.418	.00
	B	5.496		6.526		3.42		2.41		1.833	
T (nmol/mL)	A	1.221	.911	1.18	.548	1.18	.048	1.106	.00	1.055	.00
	B	1.206		1.10		0.84		0.477		0.421	

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FIGURE 2

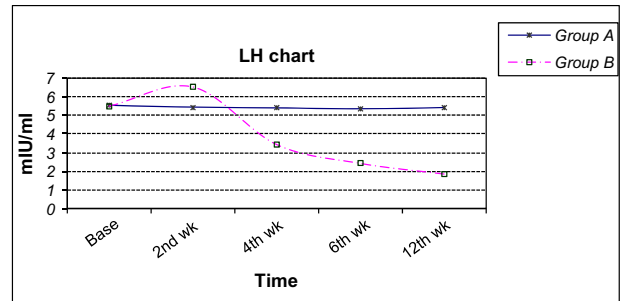
Pattern of effects of letrozole (group A) and triptorelin (group B) on serum E₂ levels during 12 weeks of treatment. Estradiol level was assessed at baseline and during treatment at weeks 2, 4, 6, and 12. There was no significant change in serum E₂ level at all visits in group A. Group B showed a small rise in the first 2 weeks, then the level declined significantly, with a maximum decrease at week 12.



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FIGURE 4

Pattern of effects of letrozole (group A) and triptorelin (group B) on serum LH levels during 12 weeks of treatment. The LH level was assessed at baseline and during treatment at weeks 2, 4, 6, and 12. There was no significant change in serum LH level at all visits in group A. Group B showed a small rise in the first 2 weeks, then the level declined significantly, with a maximum decrease at week 12.



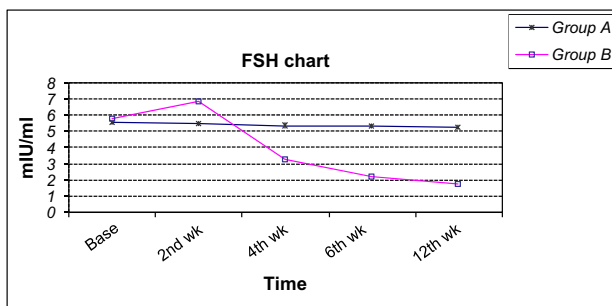
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decrease as early as the first day after aromatase inhibitor intake (39). Thus, one may expect a rapid onset of resolution of bulk-related symptoms, as seen in the Shozu et al. case report (38). Because our first measurement was 2 weeks after treatment, early (first-day) changes in hormones were not considered in our study. However, E₂ showed a little elevation at week 2 week in the GnRHa group. Furthermore, there was no initial flare-up period in the letrozole group, as occurs with GnRHa therapy. Concerning the timing of our first visit, we did not expect to observe any sign of gonadotropin flare.

Although we observed a minute and nonsignificant elevation in gonadotropins at the first visit (week 2) in the GnRHa group, Harding et al. (40) found a considerable gonadotropin flare-up and showed that concomitant hyperestrogenism might exacerbate bulk-related symptoms. They also demonstrated that increased gonadotropin levels could produce symptoms similar to the ovarian hyperstimulation syndrome, including ovarian enlargement and massive ascites, especially when GnRHa is started at the early follicular phase. Increased E levels at the initial treatment with

FIGURE 3

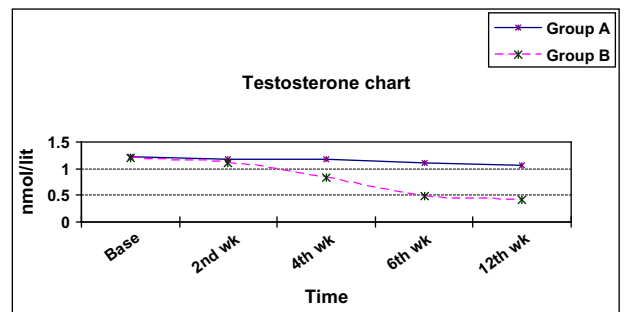
Pattern of effects of letrozole (group A) and triptorelin (group B) on serum FSH levels during 12 weeks of treatment. The FSH level was assessed at baseline and during treatment at weeks 2, 4, 6, and 12. There was no significant change in serum FSH level at all visits in group A. Group B showed a small rise in the first 2 weeks, then the level declined significantly, with a maximum decrease at week 12th.



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FIGURE 5

Pattern of effects of letrozole (group A) and triptorelin (group B) on serum T levels during 12 weeks of treatment. The T level was assessed at baseline and during treatment at weeks 2, 4, 6, and 12. There was no significant change in the serum testosterone level at all visits in group A. Group B showed a small rise in the first 2 weeks, then the level declined significantly, with a maximum decrease in week 12.



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GnRHa possibly exacerbate leiomyoma growth; although these changes are usually subtle and transient, they may result in clinical morbidity for women whose leiomyomas are already of a symptomatic size. Friedman (41) reported a case of rapid uterine enlargement and subsequent urinary retention occurring 7 days after commencement of GnRHa therapy.

We did not assess body mass index in our subjects, although a theoretical advantage of aromatase inhibitors over GnRHa reported by Hansen et al. (42) is that aromatase inhibitors are effective even in obese women who fail to respond to GnRHa therapy. They believe that in morbidly obese women, peripheral adipose tissue produces a significant amount of E through the conversion of circulating androstenedione to E, thus facilitating the growth of E-dependent tumors. Gonadotropin-releasing hormone agonist does not interfere with E synthesis in adipose tissues. In contrast, aromatase inhibitors are a theoretical choice of medical treatment because they abolish E synthesis both in the ovary and in peripheral adipose tissue simultaneously (42).

The reduction of myoma volume without hormonal changes in our group A can be explained by previous work by Shozu et al. (43) and Sumitani et al. (35). They demonstrated that leiomyoma tissues per se express high levels of E synthetase (aromatase P450), producing E in situ, which promotes their own growth through an autocrine–paracrine route. They also showed that fadrozole (aromatase inhibitor) abolishes E synthesis in leiomyoma-derived cells and inhibits the proliferation of these cells.

Mitwaly and Casper (44) showed a beneficial effect of oral administration of letrozole in the early follicular phase on ovulation in women with ovulatory infertility. In our study, letrozole was given regardless of the day of menstrual period. Moreover, we treated the subjects for a long term. That is why we did not see any changes in ovarian structure (ovarian cyst and/or significant follicular growth). To date, however, no study has reported the effects of long-term use of aromatase inhibitors on human follicular growth.

We are the first to report the long-term effects of letrozole on ovarian function.

The follow-up period of our study was too short to consider the recurrence rate of myomas after discontinuation of treatment in all subjects. Studies have reported a high recurrence rate 6 months after finishing a GnRH protocol (27, 28).

Management of uterine myoma using any type of medication (e.g., letrozole) is useful only in women for whom temporary reduction in myoma volume is aimed and no surgical intervention is planned for any reason. Women with uterine myoma who have pain, pressure effect, hypermenorrhea, or other types of abnormal uterine bleeding who wish to retain the option of childbirth; women who wish to save their uterus; women who are not fit for surgical intervention; and young women with infertility can take advantage of this type of treatment.

In conclusion, we report successful management of a series of patients with uterine myoma by use of an aromatase inhibitor. Rapid onset of action and avoidance of the initial flare-up with an aromatase inhibitor may be advantageous for short-term management of women with myomas of any size who are being managed transiently, specifically women with unexplained infertility who have uterine myoma. Letrozole may be most useful as an agent given for surgical pretreatment.

A trial comparing letrozole with uterine artery embolization may be the next most logical study.

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