

The Effect of Aromatase Inhibitor on Uterine Leiomyoma Volume by Ultrasonography and Color Doppler

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Abstract: Objective: To evaluate the effect of aromatase inhibitor (letrozole) on uterine leiomyoma size. **Study design:** Randomized clinical trial. **Setting:** Al-Zahraa University Hospital. **Patients:** Twenty premenopausal women with a single uterine myoma measuring ≥ 5 cm. They were managed with aromatase inhibitor (letrozole). **Intervention:** Study group received letrozole (2.5 mg/d) for 3 months. **Main outcome:** Measurement of myoma volume. **Results:** Total myoma volume decreased by 32.16%. Aromatase inhibitor may represent a new generation of medications for the treatment of leiomyoma. Larger clinical trials are needed however, to fully evaluate their efficacy.

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1. Introduction:

Uterine leiomyoma are the most common benign tumors of the female genital tract, often necessitating hysterectomy. The most common symptoms are dysmenorrhea, menorrhagia, infertility and abortion (*Parsanezhad et al., 2010*).

Although the aetiology of these tumors is unknown, there is no doubt that leiomyoma growth is dependent on sex steroids. Epidemiological and experimental evidences have established that ovarian hormones play an essential role in the pathogenesis of this disease. Deprivation of ovarian estrogen causes leiomyomas to shrink (*Gurates et al., 2008*). Some investigators have shown that leiomyoma tissues are a source of estrogen. Estrogen secreted by leiomyomata tissue may reach a sufficient concentration within the local compartment to support its own growth (*Bulun et al., 2005*).

Treatment options for patients with symptomatic tumors include: GnRH-a: Oral contraceptives: Mifepristone: gestrinone: selective estrogen receptor modulators (SERM): abdominal, laparoscopic or hysteroscopic myomectomy, cryotherapy, myolysis, uterine fibroid embolization and aromatase inhibitors (*Smart et al., 2006*).

Aromatase inhibitors were originally developed for the treatment of breast cancer. Letrozole is a highly potent non-steroidal aromatase inhibitor. It inhibits estrogen biosynthesis by about 99% at the dose of 2.5 mg/day (*Karaer et al., 2004*).

Adverse events associated with the use of aromatase inhibitors could include: an increase in incidence of osteoporosis, sweating, hot flashes, fatigue, aggressive behavior, adrenal insufficiency, kidney failure and liver dysfunction. Consumers with liver, kidney or adrenal abnormalities are at higher

risk for developing adverse events. The drug is contraindicated in these conditions. It is also contraindicated in women during pregnancy and lactation (*Haberfeld, 2009*).

The aim of this study was to evaluate the effects of letrozole on the size of uterine leiomyomas in premenopausal women with symptomatic uterine leiomyomas.

2-Patients and Methods

This prospective randomized study was conducted between April 2011 and September 2011, at Al-Zahraa University Hospital, Cairo, Egypt. This study enrolled twenty symptomatic premenopausal women attending the outpatient clinic having a single uterine myoma measuring ≥ 5 cm. Excluded subjects included:

- 1- Women who had additional myoma (S),
- 2- Women with uterine myoma who were under treatment with any type of estrogen or progesterone more recently than 1 month and with normal implant more recently than 3 months to exclude the effect of hormones on myoma,
- 3- Women with a history of major medical problem and/or previous medical or surgical treatment for leiomyomata,
- 4- All women with myoma measuring 2 - 5 cm,
- 5- Women with neoplastic, metabolic or infectious diseases,
- 6- History of acute or recurrent vascular thrombosis or history of blood coagulation disease,
- 7- Body mass index (BMI) > 30 kg/m²,
- 8- Endometrial abnormality or ovarian cyst detected by transvaginal ultrasound,
- 9- History of osteoporosis.

Patients who were trying to be pregnant in the following one year were also excluded.

After taking consent from all participants, all of them underwent dilatation and curettage.

Barrier contraception was used by all participants during period of study.

All subjects underwent baseline measurement, performed in the early follicular phase. Number, size, location of the leiomyomas, uterine size, ovarian sizes and endometrial thickness were assessed.

All ultrasound scans were performed by the same experienced operator using a color Doppler ultrasound machine (e saote My lab 50 X vision, Italy) with a transvaginal 6.5 MHz and transabdominal 3.5 MHz probes.

Color Doppler assessment of the uterine artery near its origin from iliac artery and fibroid arteries from the core were done and flow parameter expressed in terms of resistance index was calculated. The resistance index = peak systolic velocity _ end diastolic velocity / peak systolic velocity

After identification of the myoma, its volume was calculated. All dimension measurements were repeated twice, and the arithmetic mean was calculated. Uterine leiomyoma and ovarian volumes were calculated by applying the ellipsoid formula (length X anteroposterior diameter X transverse diameter X 0.52) (*Weeks et al., 1999*).

Measurements were performed at baseline and during treatment at weeks 4, 8 and 12 and mean values were calculated.

All women were asked to describe their menstrual patterns.

Aromatase inhibitor (Letrozole was administered orally (2.5 mg/d) for 3 months) (Femare, Novartis).

Laboratory analyses included hematological test.

The change in leiomyoma volume was the primary outcome. Changes in the endometrial thickness and haematocrit were considered as secondary outcome.

Table (1): Baseline characteristics of the study population (n=20)

Parameter	Value
Age (years)	40.92±10.4
Parity (n)	2.65±0.30
BMI (Kg/m ²)	26.20±3.61
Myoma volume (cm ³)	95.28

Table (2): Total myoma volume as percentage change from baseline in patients treated with letrozole.

Baseline	Week (4)	Decline (%)	P	Week (8)	Decline (%)	P	Week (12)	Decline (%)	P
95.28	75.879	20.4	0.05	64.46	30.8	0.02	62.65	32.6	0.02

Table (3): Endometrial thickness, haemoglobin at baseline and third month of the study

	Baseline	Week 12	P value
Hemoglobin (concentration (g/dl))	10.78±0.27	11.10±0.23	0.02
Endometrial thickness (mm)	3.5±0.18	3.53±0.14	NS

Table (4): Resistance index (RI) of uterine and fibroid arteries at baseline and third month of the study

	Baseline	Week 12	P value
RI of uterine artery	0.71±0.14	1.03±0.25	< 0.001
RI of fibroid artery	0.73±0.06	1.22±0.21	< 0.001

3. Results

The characteristics of the twenty patients studied are reported in table (1).

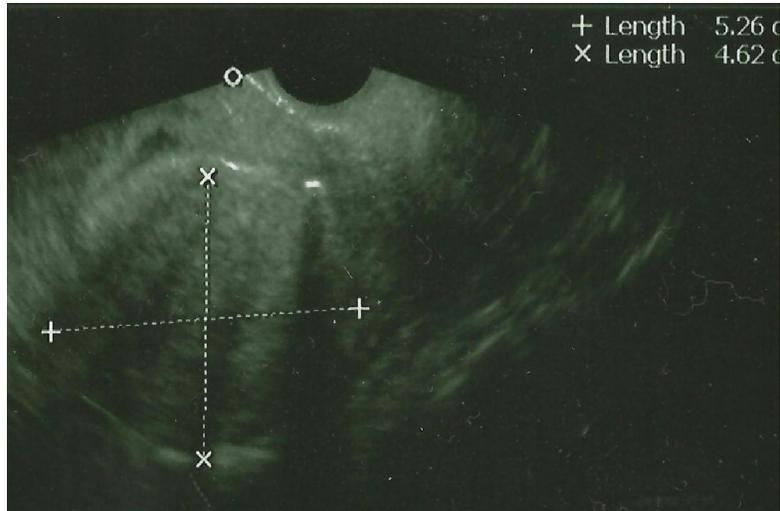
Total myoma volume is presented as the percentage change from baseline in table 2. The total myoma volume decreased by 18.32% at week 4.

It decreased by 30.8% at week 8 and it decreased by 32.6% at week 12 (p=0.02).

RI of uterine and fibroid arteries increased at week 12 in table (4).

Furthermore, hemoglobin concentrations were significantly higher at the end of the study. It increased from 10.78 to 11.10 (g/dl).

On the other hand no significant change in mean endometrial thickness was detected.



Fig(1)A

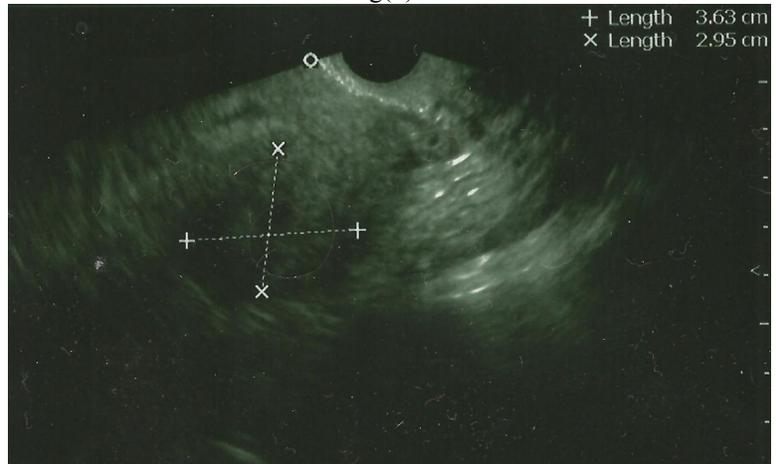


Fig:(1)B



Fig:(1)C

Fig (1): A, transvaginal ultrasonography of posterior interstitial myoma , measuring 5.2 cm in diameter before treatment . B, after 4 weeks treatment : the myoma size is 3.6 cm in diameter . C, after 8 weeks treatment : the myoma size is 2.2 cm in diameter .

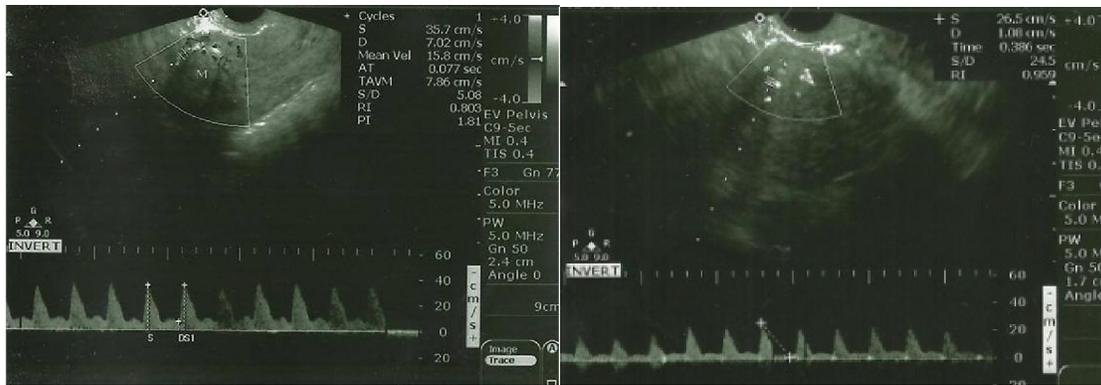


Fig (2)A

Fig (2) B

Fig (2): Color Doppler ultrasonography of fibroid artery in an interstitial myoma. A, resistance index (RI) is 0.8 at start of treatment. B, RI is 9.5 after treatment.

4. Discussion

Leiomyoma cells express a high level of aromatase P450, which is capable of synthesizing endogenous estrogen. Thus, leiomyomas produce estrogen in situ, which promotes their growth (*Shouzu et al., 2002*).

Inhibition of in situ expression of aromatase is a possible therapy for conservative management (*Varelas et al., 2007*).

In this study, treatment with letrozole resulted in a significant decrease of leiomyoma size at the end of the first treatment cycle (20.4%) ($P=0.05$). This indicates that letrozole has an effective action, with additional reduction in the next two cycles.

Also, this study demonstrated an increase of the hemoglobin concentration which may be due to an improved menstrual pattern. *Parsanezhad et al. (2010)* found that leiomyoma volume decreased by 31.7% after 4 weeks of treatment. It also decreased by 42.71%, 45.6% after 6 weeks and 12 weeks of treatment.

Gurates et al. (2008) also found a significant decrease in leiomyoma volume after treatment with letrozole. Also, they found a significant increase in hemoglobin concentration after treatment with letrozole.

The resistance index (RI) has an inverse relationship to blood flow and express impedance to flow. Doppler examination increase the confidence with which a correct diagnosis is made (*Kanelopoulos et al., 2003*).

There is strong correlation between the values of the right and left uterine artery ($P<0.001$). The mean was used. Uterine artery RI increased from 0.71 ± 0.14 to 1.03 ± 0.25 at the 3rd month of treatment. The fibroid artery RI increased from 0.73 ± 0.06 to 1.22 ± 0.21 ($P<0.001$) at the 3rd month of treatment.

Conclusion

Uterine myoma volume was successfully reduced by use of an aromatase inhibitor. Thus, aromatase inhibitors may represent a new generation for the treatment of leiomyoma. Larger clinical trials are needed to confirm this finding.

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