International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Prakash R et al. Int J Reprod Contracept Obstet Gynecol. 2017 May;6(5):2026-2030
www.ijrcog.org

pISSN 2320-1770 | eISSN 2320-1789

DOI: http://dx.doi.org/10.18203/2320-1770.ijrcog20171970

Original Research Article

Effects of letrozole on patients with symptomatic leiomyoma in the reproductive age women

Ranjana Prakash[1]*, Sushma Pandey[1], Indu Chawla[2]

[1]Department of Obstetrics and Gynecology, Patna Medical College and Hospital, Patna, Bihar, India
[2]Department of Obstetrics and Gynecology, PGIMER, Dr. Ram Manohar Lohia Hospital, New Delhi, Delhi, India

Received: 09 March 2017
Accepted: 07 April 2017

***Correspondence:**
Dr. Ranjana Prakash,
E-mail: rranjana24@gmail.com

ABSTRACT

Background: Uterine leiomyoma is a common indication for hysterectomy in India. An effective medical treatment option may reduce hysterectomy associated morbidity. This study was undertaken to evaluate the effect of the Letrozole on patients with symptomatic leiomyoma in the reproductive age women.
Methods: Prospective interventional study was conducted on 50 women between 30-45 years of age with menstrual or pressure symptoms on the bowel or urinary system, and having no. Of myoma ≤4 and size of single myoma ≥2 cms in diameter. They received tablet letrozole 5mg/day for 3 month, and effect of the drug on myoma volume and symptomatology were studied. Beside these, effects on uterine volume, ovarian volume, endometrial thickness and side effects of letrozole of any were also studied.
Results: Average reduction of myoma volume by 47.68% and uterine volume by 19.58% was seen. Haemoglobin concentration was significantly higher at the end of study. It increased from 9.56g/dl to 10.76g/dl and overall improvement in symptomatology score was observed. Ovarian volume increased significantly from baseline mean volume of 8.18±0.51cm³ to 19.3±0.84cm³ and no significant change in endometrial thickness was observed at the end of 3 month. Sweating, hot flushes, nausea and vomiting were the main adverse effects observed and were self limiting.
Conclusions: Letrozole, the aromatase inhibitor resulted in significant volume reduction of the uterus-leiomyoma structure and was effective in controlling the more frequent symptoms of this disorder with fewer side effects.

Keywords: Aromatase inhibitor, Letrozole, Medical treatment, Myoma, Uterus

INTRODUCTION

Uterine Leiomyomas are the commonest benign gynaecological tumours occuring in up to 25 per cent of women in reproductive age group and in about 40 per cent, symptoms are severe enough to warrant therapy.[1] The definitive treatment for symptomatic myomas has always been surgical and myomas account for up to 40 per cent of all hysterectomies in pre-menopausal women.[2]

Treatment modalities for symptomatic myomas other than surgery include - myolysis, embolization of feeding arteries (invasive), GnRH agonist and antagonists, selective oestrogen receptor modulators [SERM], danazole, gestrinone, anti-progestogens and aromatase inhibitors.[3] But these have certain limitations. Danazol reduces uterine volume by 18-23 percent but is associated with marked androgenic side-effects and liver dysfunction.[4] Gonadotrophin releasing hormone agonist (GnRH) reduces leiomyoma size to about 50 per cent in 3 month but is expensive, has to be given parenterally and is also associated with hypoestrogenism leading to hot flushes, vaginal dryness and bone loss.[5,6] Uterine artery embolization has been shown to decrease leiomyoma size by 35-69 per cent, improve menorrhagia and reduce pain,

but there are potential risks of premature ovarian failure and uterine synechia.[7]

Although the aetiology of these tumours 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 oestrogen causes leiomyoma to shrink.[8] Some investigators have shown that leiomyoma tissues are a source of oestrogen. Oestrogen secreted by leiomyomatous tissue may reach a sufficient concentration within the local compartment to support its own growth.[9] The capacity of local oestrogen production is linked to the elevated activity of the aromatase enzyme, identified in this tumour.[10]

Aromatase inhibitors were originally developed for the treatment of breast cancer. Letrozole is a highly potent non-steroidal aromatase inhibitor. It inhibits oestrogen biosynthesis by about 99% at the dose of 2.5 mg/day.[11] The aim of the present study was to evaluate the effects of letrozole on the size of the uterus and on the size and symptoms of uterine leiomyomas in the reproductive age women.

METHODS

After approval by the Hospital Ethical Committee, this prospective study was conducted in the department of Obstetrics and Gynaecology at Patna Medical College and Hospital, Patna over a period of 2 years from October 2011 to September 2013. 60 women between 30-45 years of age with menstrual or pressure symptoms on the bowel or urinary system, and having number of myoma ≤4 and size of single myoma ≥2cm in diameter on ultrasound were included in the study. Patients with neoplastic, renal, liver, haematological and infectious disease, oral administration of any type oestrogen and progesterone in previous 3 month, BMI≥30kg/m^2, history of previous deep venous thrombosis or coagulopathy, history of osteopenia or osteoporosis, ovarian cyst detected by Transvaginal ultrasound (TVS), endometrial abnormalities on dilatation and curettage or by TVS were excluded from study. Patients with uterine leiomyomas who requested immediate surgical treatment or who were trying to become pregnant in the following one year were also excluded.

Patients fulfilling the inclusion criteria were informed about advantages and side- effects of letrozole use, and were counselled and advised to use barrier methods of contraception during entire study period. After informed consent, demographic and baseline clinical profile including details of menstrual cycle, symptoms and their severity was noted and accordingly symptomatology score determined. It is an objective assessment of the symptoms related to uterine myoma taking into account the menstrual volume, duration of flow, presence or absence of dysmenorrhoea and pressure symptoms with sum total of four to twelve point as shown in Table 1.[12]

Table 1: Scoring system used to evaluate the symptomatology.

Score	Menstrual volume	Duration of menstruation (days)	Dysmenorrhoea	Pressure symptoms
1.	Normal	3-7	Absent	Absent
2.	Increased	>7	Mild	Mild
3.	Heavy	Menorrhagia/ Metrorrhagia	Disabling	Severe

A complete general and gynaecological examination was done. Laboratory analyses included complete haemogram, Renal and Liver function test, thyroid profile, blood sugar, bleeding time and clotting time. All participants underwent dilatation and curettage before entering the study. After complete evaluation, all women were prescribed to take tab. Letrozole 5mg/day continuously for 3 month (Femara, Novartis).

A detailed baseline transvaginal ultrasound was done on all patients in the early follicular phase to know the exact size and volume of uterus, number, size, volume and location of myomas, volume of ovary and endometrial thickness at the start of treatment. A repeat ultrasound was done after completion of therapy for 3 month. TVS was performed by the same experienced operator using Toshiba model ultrasonography machine with a transvaginal 6.5 MHZ probe. Uterine, leiomyoma and ovarian volume was measured by applying Ellipsoid Formula V- D1×D2×D3×.52. Where D1, D2 and D3 are the longitudinal, transverse and cross-sectional diameter of the fibroid respectively.[13] When 2 or > leiomyomas were detected, the arithmetic mean was used.

Lumbar spine bone mineral densities were also measured with the use of DEXA SCAN (dual energy x-ray absorptiometry) at the initiation of therapy and at the end of 3 month, to determine any loss of bone mineral density.

Patients were followed at 3 month after stopping therapy, complete hemogram was repeated. Patients were asked about improvement or deterioration of symptoms and note was made of any adverse effects, and underwent clinical examination for uterine size.

The change in leiomyoma volume was the primary outcome. Secondary outcomes like Changes in the uterine volume, ovarian volume, endometrial thickness, haemoglobin percentage, lumbar spine bone mineral densities and side-effects if any were also noted.

RESULTS

Total 60 cases were enrolled for study. 10 women left treatment (drop-out rate -17%) while rest 50 completed the 3 months treatment protocol. Reasons for drop out cannot be commented as they never reported back to us during the study period of 2 years. Baseline characteristics are shown in Table 2.

Table 2: Baseline characteristics of study population (n=50).

Parameters	Value
Age (years)	39.9±23.72
Parity (n)	3.08±3.16
BMI (kg/m^2)	23.66±2.79
Myoma volume (cm^3)	65.74±30.58

Abnormal and excessive uterine bleeding (AUB) was the commonest problem reported by 38 cases (76%) followed by dysmenorrhoea in 28 (56%) and urinary frequency and others in 10 (20%) for which they came to the hospital.

Among AUB, 62% had menorrhagia, 26% poly-menorrhagia, and 12% reported to have menometrorrhagia. At enrollment, the symptomatology scores were 4-6, 7-9 and 10-12 in 20 (40%), 28 (56%) and 2 (4%) of women respectively as shown in Table 3.

Table 3: Symptomatology scores after letrozole treatment.

Symptomatology score	Day 0	At the end of 3 month
4-6	20	36
7-9	28	14
10-12	2	0

In this study, mean uterine volume decreased by 19.58% ($p<0.01$), while mean volume of dominant leiomyoma decreased by 47.68% ($p<0.01$) after three months of complete treatment.

But, ovarian volume increased significantly ($P<0.01$), this happened probably because letrozole promotes the overall growth of ovary, including follicular growth. Furthermore, hemoglobin concentrations were significantly higher at the end of the study. It increased from 9.56g/dl to 10.76g/dl. On the other hand no significant change in mean endometrial thickness was detected, as shown in Table 4.

Table 4: Clinical outcomes after letrozole treatment.

Parameters	Baseline	At the end of 3 month	Changes	p-value
Mean value of myoma volume (cm^3)	65.74±30.58	34.39±17.3	47.68% fall	<0.01
Mean value of uterine volume (cm^3)	177±13.72	142.34±11.35	19.58% fall	<0.01
Mean value of ovarian volume (cm^3)	8.18±0.51	19.37±0.84	136.79%rise	<0.01
Mean value of Hb% (g/dl)	9.59±1.26	10.76±0.85	12.20% rise	<0.01
Mean value of endometrial thickness (mm)	4.05±0.45	4.04±0.44	No significant changes	0.258

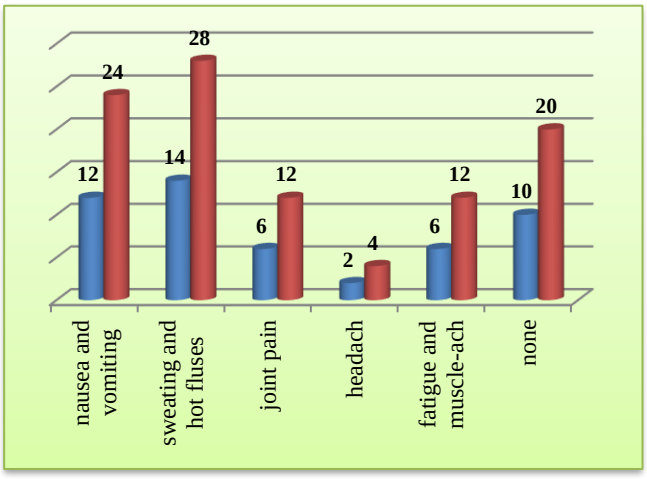

Figure 1: Side-effects of letrozole.

Sweating and hot flushes were noted in 28% of patients, nausea and vomiting occurred in 24%. Twelve percent of the cases complained of joint pain, fatigue and muscle ach and headache in 4% of the patients. No side-effects were observed in rest 20 % of patients. However, none of the patients discontinued the therapy because of side effects, as shown in Figure 1.

In this study, all the patients were advised DEXA-SCAN at the beginning and at the end of study and t-score value was evaluated to know any evidence of osteopenia or osteoporosis. But, among 50 patients which were selected for study, only 25 Patient was willing for DEXA-SCAN, probably because of their high cost. Baseline t-score among these 25 patient was within normal range (-1 to +1) and no change was found at the end of treatment.

However, the result was inconclusive because t-score value was not evaluated in remaining 25 patients.

DISCUSSION

Oestrogen concentration in leiomyoma has been reported to be elevated because of the capacity of local oestrogen production in the myomatous tissue, promoted by the paracrine action of this hormone, which enables the myoma to partly control its own growth.[14] Leiomyoma cells also express a high level of aromatase 450, which catalyzes the conversion of androgen to oestrogen; they would logically appear to have a role in the management of these tumours. Use of aromatase inhibitors in the treatment of uterine leiomyoma appears to offer a series of advantages over the analogues of GnRH which have been tried extensively for this condition.[15] The differential inhibition of oestrogen synthesis in the leiomyoma and ovary can reduce the volume of the tumour, without the systemic adverse effects observed with GnRH analogues (phenomenon of flare-up and menopausal symptoms in general).

This concept was first used by Shozu et al, who used fadrozole 2mg once a day for 8 weeks in perimenopausal women and recorded a 71% reduction in myoma size.[16] Apart from this, many other studies have reported on the use of various aromatase inhibitors in this condition with variable results.

In this study, the volume of myoma decreased significantly from baseline mean value of 65.74±30.50cm³ to 34.39±17.3cm³ at the end of treatment. Parsanezhad et al. used letrozole in a daily dose of 2.5 mg for 12 weeks and found reduction in leiomyoma volume by 31.7%, 42.71% and 45.6% after 4 weeks, 6 weeks and 12 weeks of treatment with letrozole respectively.[17] Gurates et al reported that at the end of 3 month, letrozole resulted in a mean 46.72% reduction of original uterine leiomyoma volume and mean reduction of original uterine volume by 21.67% whereas Hilario SG et al reported that there was average reduction of uterine volume of 9.32% attaining up to 30% with the use of anastrazole 1 mg/day over 12 weeks.[8,12]

This study also demonstrated an increase in the haemoglobin concentration which may be due to an improved menstrual pattern. Baseline mean value of haemoglobin concentration was 9.59±1.26 g/dl and at the end of treatment it was 10.76±0.85 g/dl and hence statistically significant ($p < 0.01$). The symptomatology scores were 4-6, 7-9 and 10-12 in 72%, 28% and 0% of the cases at the end of 3 month and hence, overall improvement in scores were observed. Baseline mean value of endometrial thickness on day 4 of cycle was 4.04±0.45 mm and no significant change in endometrial thickness was detected at the end of treatment.

In the present study, ovarian volume increased significantly ($p<0.01$) from baseline mean value of 8.18±0.51cm³ to 19.3±0.84cm³ at the end of 3 month. In present study, we had not done TVS of patients at every month and results were also not evaluated monthly, but overall significant increase in ovarian volume was seen. Gurates et al, reported that left ovarian volume was significantly ($P<0.01$) increased compared with baseline for each month of therapy except for the first month, right ovarian volume was significantly ($p<0.01$) increased only for the third month.[18] Administration of letrozole to cycling female rats caused a dose dependent inhibition of uterine weight and a statistically significant increase in ovarian weight.[19]

Overall no loss of bone mineral density was seen at the end of treatment with letrozole among 25 patients who undergone DEXA-SCAN. Gurates et al reported no loss of bone mineral density with letrozole use, found as advantage over GnRH agonist. Short-term use of aromatase inhibitor has no clear effects on the bone mineral density (BMD) though long term use may result in its loss.[20] In the present study, therapy was given for a very short duration of 3 months and is unlikely to have caused a significant and measurable loss of BMD.

Administration of letrozole in the early follicular phase is known to increase gonadotropin secretion and hence follicular recruitment and ovulation, thus increasing the risk of pregnancy.[21] Sex steroids might affect the beneficial and therapeutic effects of Letrozole. So, in this study oral contraceptive or progestin were not used as a method of contraception. With the use of barrier method of contraception, no conception was noted in the present study. This study was designed for a short duration of 3 month and post-treatment follow up could not be done. So, long term effects of letrozole were not evaluated on regrowth of myoma and re-occurrence of symptoms.

CONCLUSION

Letrozole, the aromatase inhibitor used in symptomatic women of reproductive age group resulted in volume reduction of the uterus-leiomyoma structure and was effective in controlling the more frequent symptoms of this disorder with fewer side effects.

ACKNOWLEDGEMENTS

The authors take this opportunity to thank all the patients without whose cooperation the study could not have been conducted and they also appreciate Dr. Pramod Kumar, senior resident, Department of Radiology, Patna Medical College and Hospital, Patna for performing TVS on all patients and assisting in interpretation of the results at the end of study.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Adamson GD. Treatment of uterine fibroids: current findings with gonadotropin-releasing hormone agonists. Am J Obstet Gynecol. 1992;166:746-51.
2. Carlson KJ, Nichols DH, Schiff I. Indications of hysterectomy. N Engl J Med. 1993;328:856-60.
3. Smart OC, Hindley JT, Regan L and Gedroyc WG. Gonadotrophin-releasing hormone and magnetic-resonance guided ultrasound surgery for uterine leiomyomata. Obstet Gynecol. 2006;108:49-54.
4. Delco V la Marca A, Margante G. Short term treatment of uterine fibromyomas with danazole gynecol. Obstet Invest.1999;47:258-62.
5. Stovall TG, Summit RL, Jr, Washburn SA, Ling FW. Gonadotropin- releasing hormone agonist use before hysterectomy. Am J Obstet Gynecol. 1994;170:1744-51.
6. Lethaby A, Vollenhoven B, Sowter M. Preoperative GnRH analogue therapy before hysterectomy or myomectomy for uterine fibroids. Cochrane Database Syst Rev. 2001:CD000547.
7. Pron G, Cohen M, Soucie J, Garvin G, Vanderburgh L, Bell S. The Ontario Uterine Fibroid Embolization Trial. Part 1. Baseline patient characteristics, fibroid burden, and impact on life. Fertil Steril. 2003;79:112-9.
8. Gurates B, Parmaksiz C, Kilic G, Celik H, Kumru S, and Simsek M. Treatment of symptomatic uterine leiomyoma with letrozole. Reprod Biomed Online. 2008;17:569-74.
9. Bulun SE, Imir G, Utsunomiya H, Thung S, Gurates B, and Tamura M. Aromatase in endometriosis and uterine leiomyomata. J Steroid Biochem Mol Biol. 2005;95:57-62.
10. Andersen J, DyReys VM, Barbieri RL, Cochman DM, Miksicek RJ. Leiomyoma primary cultures have elevated transcriptional response to Invest 1995;2:542-51.
11. Karaer O, Oruc S and Koyuncu FM: Aromatase inhibitors: possible future applications. Acta Obstet Gynecol Scand. 2004;83:699-706.
12. Hilario SG, Bozzini N, Borsari R, Baracat EC. Action of aromatase inhibitor for treatment of uterine leiomyoma in perimenpausal patients. Fertil Steril. 2009;91(1):240-3.
13. Weeks AD, Duffy SR and Walker JJ. Uterine ultrasonographic changes with gonadotropin-releasing hormone agonists. Am J Obstet Gynecol. 1999;180:8-13.
14. Sumitani H, Shozu M, Segawa T, Murakami K,Yang H, Shimada K, etal. In situ oestrogen synthesized by aromatase p450 in uterine leiomyoma cells promotes cell growth probably via an autocrine/intracrine mechanism. Endocrinol. 2000;141:3852-60.
15. Shozu M, Murakami K, Inoue U. Aromatase and leiomyoma of the uterus. Semin S Reprod Med. 2004;22:55-61.
16. Shozu M, Murakami K, Segawa T, Kesal T, Inoue M. successful treatment of a symptomatic uterine leiomyoma in a premenopausal women with a non steroidal aromatase inhibitor. Fertil Steril. 2003:79:628-31.
17. Parsanezhad ME, Azmoon M, Alborzis S, etal. 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. Fertil Steril. 2010;74:192-8.
18. Sinha S, Kaseta J, Santner SJ, Demers LM, Bremmer WJ, Santen RJ. Effect of CGS 20267 on ovarian aromatase and gonadotropin levels in the rat. Breast Cancer Res Treat. 1998;48:45-51.
19. Yosry LM, Hamed E, El Naggar AA. The effect of aromatase inhibitor on uterine leiomyoma volume by ultrasonography and colour Doppler. J Am Sci. 2012;8(8):1031-4.
20. Kumru S, Yildiz AA, Yilmaz B, Sandal S, Gurates B. Effects of aromatase inhibitors letrozole and anastrazole on bone metabolism and steroid hormone levels in intact female rats. Gynecol Endocrinol. 2007;23:556-61.
21. Mitwally MF, Casper RF. Use of aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. Fertil Steril. 2001;75:305-9.

Cite this article as: Prakash R, Pandey S, Chawla I. Effects of letrozole on patients with symptomatic leiomyoma in the reproductive age women. Int J Reprod Contracept Obstet Gynecol 2017;6:2026-30.