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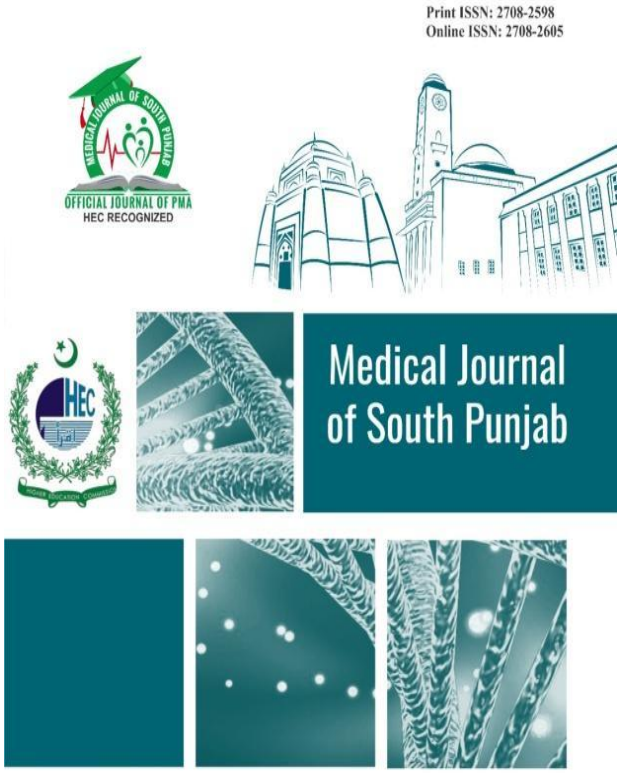

Effect of Letrozole on shrinking the size of uterine fibroids in symptomatic patients of the reproductive age group

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Original Article

Effect of Letrozole on shrinking the size of uterine fibroids in symptomatic patients of the reproductive age group

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ABSTRACT

Objective: To compare the mean fibroid size (cm) before and after treatment with letrozole and the frequency of symptom improvement in symptomatic patients of the reproductive age group.

Methodology: Quasi-experimental study was conducted between November 1st, 2024, and April 30th, 2025, at the Obstetrics and Gynaecology Department of Nishtar Hospital in Multan. Thirty women aged 25-45 who presented to the outpatient department were enrolled in this study. Throughout the trial, married women were encouraged to use barrier methods of contraception. Symptoms were graded according to the operational definition. Every woman took 5mg of the tablet Letrozole daily for three months. The size of the myoma before and after treatment, as well as the improvement in symptoms, was recorded.

Results: The mean age of the study population was 34.70 ± 5.31 years. Most patients were married (76.7%, n = 23), had 0–2 children (66.7%, n = 20), and were non-obese (73.3%, n = 22). Leiomyomas were primarily single in 63.3% (n = 19) of patients, with a mean size of 4.63 ± 1.22 cm, and 60.0% (n = 18) exceeded 5 cm. Letrozole therapy significantly reduced uterine fibroid size from 5.37 ± 0.88 cm (pre-treatment) to 4.64 ± 0.70 cm (post-treatment), with a mean reduction of 0.73 cm ($p = 0.003$). Among 30 patients, 66.7% (n = 20) reported symptom improvement after receiving letrozole therapy.

Conclusion: Reduced uterus-leiomyoma size, improved control of related symptoms, and fewer adverse effects were observed after treatment with Letrozole.

Key Words:*Fibroid; Leiomyoma; Letrozole; Uterine fibroids; Fibroid Uterus; Aromatase Inhibitors*

1. INTRODUCTION

Up to 25% of women of childbearing age have uterine leiomyomas, making it the most

common benign gynaecological tumour. Approximately 40% of these instances involve severe symptoms that warrant medical attention.[1] Surgery has long been the mainstay of treatment for symptomatic myomas [2]. In addition to surgical removal, symptomatic myomas can be treated with myolysis, embolization of feeding arteries (invasive), GnRH agonists and antagonists, selective estrogen receptor modulators [SERM], danazol, gestrinone, anti-progestogens, and aromatase inhibitors [3]. However, due to their unfavourable consequences, they are subject to certain limitations [4].

Epidemiological and experimental evidence indicate that ovarian hormones play a crucial role in the development of uterine fibroids. When ovaries aren't producing as much estrogen, leiomyomas tend to diminish.[5] The estrogen secreted by leiomyomatous tissue may accumulate to a level sufficient to sustain its proliferation within the local compartment.[6] In this tumor, increased activity of the aromatase enzyme was associated with the local estrogen synthesis ability.[7] Aromatase inhibitors were first created to combat breast cancer. Letrozole is one of the most effective non-steroidal aromatase inhibitors available. Approximately 99% of estrogen production is blocked [8].

Parakash et al conducted a study on 50 symptomatic women aged between 30 and 45 years with leiomyomas. They received letrozole 5mg/day for 3 months—an average reduction in myoma volume of 47.68% and uterine volume of 19.58%.[9] Duhan et al studied the effect of letrozole on myoma size, volume, and symptomatology in 30 premenopausal women aged between 30 and 55 years. At the end of 3 months, the mean myoma size had reduced from 5.4 ± 1.3 cm to 4.3 ± 0.9 cm ($p < 0.05$), and the myoma volume exhibited a reduction of 52.45% ($p = 0.00$).[10] The present study aims to determine the role of letrozole in reducing the size of uterine fibroids and the uterus in symptomatic reproductive-age women presenting in our local setting. The study will help establish the beneficial role of letrozole in cases of uterine fibroids, enabling treating gynaecologists to use the drug based on evidence for the maximum benefit of their patients. Previously, no such study had been reported in our local region.

2. METHODOLOGY

Following the approval of the institutional ERB (3601/NMU; date: 13-02-2025), this Quasi-experimental (pre-post intervention) study was conducted at the Department of Obstetrics and Gynaecology, Nishtar Hospital, Multan, from November 1, 2024, to April 30, 2025. Data was collected through Non-Probability Consecutive Sampling. A total of 30 cases were studied, with a 5% margin of error, a 95% confidence level, and a 50% response rate. Women aged 25–45 who were willing to participate had myomas with a diameter of more than 4 cm on ultrasonography, a duration of less than three months, and the presence of symptoms were included. Patients who requested emergency surgery, were trying to conceive within the next year, had a documented history of deep vein thrombosis or coagulopathy, osteopenia or osteoporosis, or had taken estrogen and progesterone in pill form within the past three months were excluded. Data were collected over six months, and baseline demographic data, including age, marital status (married / not married), parity, and obesity, were noted. Throughout the studies, researchers encouraged married women to use barrier methods of contraception. An operational definition was employed to quantify the severity of the symptoms. The myoma size before and after treatment, as well as the improvement in symptoms, were recorded according to the operational definition. All the data was recorded on the proforma. All patients underwent TVS before and after therapy using a Toshiba model ultrasonography machine and a transvaginal 6.5 MHz probe, with the same skilled operator performing both exams. For three months,

each woman received 5 milligrams of Letrozole orally, once a day.

The statistical data were evaluated via SPSS version 23. Patients were assessed for the outcome, such as mean fibroid size (cm) before and after treatment with letrozole and frequency of symptom improvement in symptomatic patients of the reproductive age group, using a paired t-test, and stratification was done to overcome confounders

3. RESULTS

The study included 30 patients with a mean age of 34.70 ± 5.31 years, predominantly aged 25–35 (56.7%). Most patients were married (76.7%, n = 23), had 0–2 children (66.7%, n = 20; mean parity: 2.20 ± 0.66), and were non-obese (73.3%, n = 22). Leiomyomas were primarily single in 63.3% (n = 19) of patients, with a mean size of 4.63 ± 1.22 cm, and 60.0% (n = 18) exceeded 5 cm (Table 1).

Letrozole therapy significantly reduced uterine fibroid size from 5.37 ± 0.88 cm (pre-treatment) to 4.64 ± 0.70 cm (post-treatment), with a mean reduction of 0.73 cm (*paired t-test*: t = 3.30, p = 0.003). (Figure 1). Among 30 patients, 66.7% (n = 20) reported symptom improvement after letrozole therapy, while 33.3% (n = 10) experienced no improvement. (Figure 2).

Patients aged 25–35 showed a decrease in fibroid diameter (5.41 ± 0.79 cm to 5.31 ± 1.01 cm; p = 0.010), whereas those aged 36–45 showed no significant change (p = 0.098). Married patients exhibited an increase in size (5.34 ± 0.98 cm to 5.46 ± 0.43 cm; p = 0.021), while single patients showed a trend toward a reduction (p = 0.047). Patients with ≥3 children demonstrated significant shrinkage (4.68 ± 0.82 cm to 4.55 ± 0.42 cm; p = 0.010), as did obese individuals (5.56 ± 0.79 cm to 5.30 ± 0.92 cm; p = 0.019). (Table 2).

Chi-square tests showed non-significant differences across all variables: age (25–35 years: 55.0% improved vs. 60.0% non-improved, p=0.794), marital status (married: 80.0% vs. 70.0%, p=0.542), parity (0–2 children: 70.0% vs. 60.0%, p=0.584), and obesity (25.0% vs. 30.0%, p=0.770) (Table 3).

Table 1: Demographics and clinical characteristics of the patients

Characteristics	N (%)	Mean ± S.D
Age (years)		34.70 ± 5.31
25-35	17 (56.7)	
36-45	13 (43.3)	
Marital Status		
Married	23 (76.7)	
Single	10 (23.3)	
Parity		2.20 ± 0.66
0-2	20 (66.7)	
≥3	10 (33.3)	
Obesity		
Yes	8 (26.7)	
No	22 (73.3)	
No of leiomyomas		1.37 ± 0.49
Single	19 (63.3)	
Multiple	11 (36.7)	
Size of leiomyomas (cm)		4.63 ± 1.22
≤5	12 (40.0)	
>5	18 (60.0)	

Figure 1: Effect of letrozole therapy on uterine fibroid size

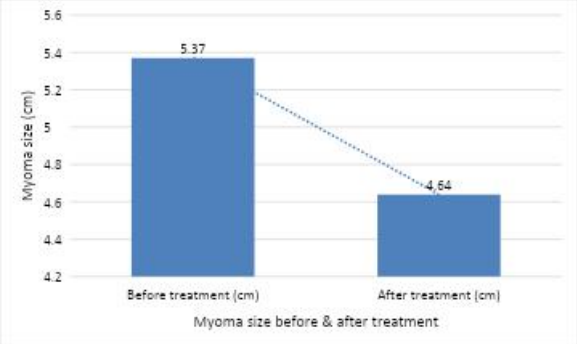

Figure 2: Improvement of symptoms of patients

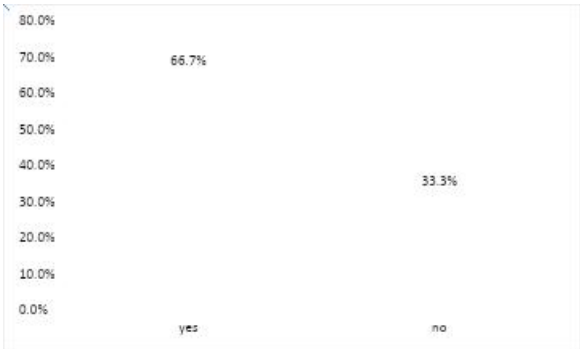

Table 2: Effect of letrozole therapy on leiomyoma size: stratified analysis by demographic and clinical characteristics

Group	Subgroup	Leiomyoma diameter(cm)		Paired t-test	p-value
		Before treatment	**After treatment**		

		Mean ± S.D	**Mean ± S.D**		
Age (years)	25-35	5.41±0.79	5.31±1.01	2.93	**0.010**
	36-45	4.68±0.52	4.58±0.91	1.79	0.098
Marital Status	Married	5.34±0.98	5.46±0.43	2.49	**0.021**
	Single	4.67±0.73	4.51±0.65	2.48	0.047
Parity	0-2	5.15±0.66	5.81±1.11	1.82	0.084
	≥3	4.68±0.82	4.55±0.42	3.25	**0.010**
Obesity	Yes	5.56±0.79	5.30±0.92	2.54	**0.019**
	No	4.73±0.43	4.60±0.78	2.19	0.064

Table 3: Association of demographic and clinical characteristics with symptom improvement

Group	Subgroup	Improvement of symptoms		Chi-square	p-value
		Yes	**No**		
Age Groups	25-35	11 (55.0)	6 (60.0)	0.068	0.794
	36-45	9 (45.0)	4 (40.0)		
Marital Status	Married	16 (80.0)	7 (70.0)	0.38	0.542
	Single	4 (20.0)	3 (30.0)		
Parity	0-2	14 (70.0)	6 (60.0)	0.300	0.584
	≥3	6 (30.0)	4 (40.0)		
Obesity	Yes	5 (25.0)	3 (30.0)	0.085	0.770
	No	15 (75.0)	7 (70.0)		

4. DISCUSSIONS

Due to the tumour's ability to partially govern its growth via the paracrine action of this hormone and consequent local estrogen production in the myomatous tissue, elevated estrogen levels have been observed in leiomyomas. Additionally, leiomyoma cells contain a high level of aromatase P450, an enzyme that converts androgens into estrogens.[11] Aromatase inhibitors, which prevent androgens from being converted into estrogen, show promise as a treatment for cancer. Aromatase inhibitors offer advantages for treating uterine leiomyoma compared to GnRH analogues, which have been extensively investigated for this condition.[12] Three months of treatment with up to ten times the recommended dose of a highly selective, third-generation aromatase inhibitor resulted in no change in cortisol or aldosterone levels.[13] In addition, they do not affect lipid profiles or induce androgenic, progestagenic, or estrogenic side effects, including fatty tissue accumulation, acne, or hypertrichosis [14,15]. By selectively blocking estrogen synthesis in the ovary and leiomyoma, tumor volume can be reduced without the systemic side effects seen with GnRH analogues (the "flare-up" phenomenon and other menopausal symptoms). Thus, aromatase inhibitors completely restrict estrogen production in the leiomyoma, while only partially suppressing estrogen production in the ovary.[16]

In our study, the size of the myoma decreased significantly from the mean value of 5.373±0.8cm to 4.64±0.7cm after 3 months of treatment with letrozole therapy of 5mg/day. The symptoms associated with uterine fibroids were improved in 20 patients (66.7%). Leiomyoma volume was reduced by 31.7% after 4 weeks of treatment with letrozole, 42.71% after 6 weeks of treatment, and 45.6% after 12 weeks of therapy in a study by Parsanezhad et al.[17]. In contrast, our study showed a reduction of only 14% after 12 weeks. In another study in Lahore, the volume of leiomyoma decreased from a mean value of 31.28±6.76mm to 10.42±4.7mm ($p < 0.01$) after 3 months of treatment with letrozole therapy. In another study in China, treatment with letrozole resulted in a 16% reduction in leiomyoma volume, which is consistent with our findings.[19]

Patients aged 25–35, single patients, patients with ≥3 children, and obese individuals showed a reduction in tumour size in patients undergoing letrozole therapy. The responsiveness of letrozole in younger patients was consistent with a study conducted by Cook et al. [20]. An interesting factor of increasing tumour size in married females suggests that although marital status is not a biological determinant, it may correlate

with factors such as sexual activity, hormonal fluctuations, or stress levels, which could influence fibroid dynamics. However, further research is needed to elucidate the underlying mechanisms of this association.

The understanding that higher parity is associated with reduced estrogen exposure over time, potentially enhancing the efficacy of aromatase inhibitors, such as letrozole. The hormonal milieu in multiparous women may thus render fibroids more susceptible to medical therapy [21]. Our study has some limitations, including its relatively short duration (3 months) and the inability to undertake post-study follow-up. Therefore, the long-term effects of letrozole on myoma regrowth and symptom recurrence are unknown. Hence, further studies with a larger sample size and extended follow-up are recommended at various doses of letrozole.

5. CONCLUSIONS

This research suggests that premenopausal women with leiomyomas larger than 4cm who are experiencing symptoms may benefit from taking the aromatase inhibitor letrozole. The drug's lack of serious side effects makes it an attractive potential treatment choice. However, we stress the importance of conducting larger-scale experiments.

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