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Original Research Article

Letrozole plus metformin versus letrozole alone in the treatment of symptomatic endometrioma

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ABSTRACT

Background: Endometriosis is a chronic, estrogen-dependent inflammatory disorder affecting up to 10% of reproductive-age women, with endometrioma present in 17-44% of cases and linked to pain and subfertility. This study aims to compare the efficacy of letrozole plus metformin versus letrozole alone in the treatment of women with symptomatic endometrioma. The aim of the study was to evaluate the efficacy of letrozole plus metformin versus letrozole alone in reducing endometrioma size, pain, and serum IL-6 levels, with comparable side effects.
Methods: This randomized controlled trial (RCT) was conducted at the department of reproductive endocrinology and infertility, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka (January 2022 to June 2023). Fifty women with endometrioma (<5 cm) received either letrozole (2.5 mg/day) plus metformin (1500 mg/day) or letrozole alone for 12 weeks. Outcomes (endometrioma size, visual analog scale (VAS) pain score, IL-6 levels) were analyzed using SPSSv23 (paired/unpaired t tests; $p<0.05$ significant).
Results: Letrozole plus metformin (Group A) and letrozole alone (Group B) were compared in 50 women with endometrioma, with no significant baseline differences ($p>0.05$). After 3 months, group A showed greater reduction in endometrioma size ($p=0.003$), pain scores, and IL-6 levels, though the latter two were not statistically different between groups ($p>0.05$). Side effects were mild and similar in both groups, indicating improved efficacy of the combination therapy with comparable safety.
Conclusions: Combined letrozole and metformin therapy significantly reduces endometrioma size, pain, and IL-6 levels more than letrozole alone, offering a promising treatment for endometriosis patients seeking fertility.

Keywords: Letrozole, Metformin, Endometrioma

INTRODUCTION

Endometriosis is defined as the presence of endometrial glands and stroma outside the uterine cavity, affecting approximately 10% of women of reproductive age.[1,2] Among infertile women, the prevalence ranges from 25% to 40%.[3] It is an estrogen-dependent, chronic inflammatory disorder that may lead to dysmenorrhea, dyspareunia, chronic pelvic pain, formation of endometrioma, and subfertility.

An endometrioma is a cystic ovarian lesion lined by ectopic endometrial tissue and is observed in 17% to 44% of patients with endometriosis.[4] The exact pathophysiology of endometriosis remains uncertain, although retrograde menstruation and implantation of

endometrial cells (Sampson's theory) is the most widely accepted explanation.[5] Additional contributing factors include immune dysfunction, hormonal imbalances, oxidative stress, and environmental toxins. Estrogen is a key hormone involved in both the initiation and maintenance of endometriosis.[6] Endometriotic lesions express aromatase and 17β-hydroxysteroid-dehydrogenase type 1-enzymes that promote local estrogen biosynthesis-but are deficient in 17β-hydroxysteroid-dehydrogenase type 2, which inactivates estrogen.[7]

Immune system dysfunction and persistent inflammation are also central to the pathogenesis of endometriosis. Elevated levels of pro-inflammatory cytokines such as IL-6 and IL-8 promote disease progression, while matrix metalloproteinases (MMPs) and vascular endothelial growth factor (VEGF) contribute to tissue invasion and angiogenesis.[8,9]

Treatment of endometrioma involves both surgical and medical approaches. Laparoscopic excision is widely practiced but may compromise ovarian reserve and is costly. Medical therapy aims to suppress estrogen and inflammation. While drugs such as progestins, danazol, oral contraceptives, dienogest, and GnRH analogs can reduce symptoms and lesion size, they inhibit ovulation and have adverse effects, limiting long-term use.

Newer pharmacologic options such as letrozole and metformin are being explored for endometriosis due to their efficacy, tolerability, and minimal impact on ovulation. Endometriotic tissue contains steroid receptors and expresses aromatase, the key enzyme in estrogen biosynthesis. Aromatase activity is minimal in normal endometrium but elevated in endometriotic lesions.[10] Estrogen stimulates prostaglandin E2 (PGE2) synthesis, which further upregulates aromatase in a self-perpetuating cycle.[11] Aromatase inhibitors like letrozole interrupt this cycle, targeting both ovarian and ectopic estrogen production-unlike conventional therapies, which act only at the ovarian level.[12] Letrozole, a third-generation nonsteroidal aromatase inhibitor, selectively inhibits aromatase and may contribute to regression of endometrioma.

In a study by Madny et al letrozole significantly improved endometriosis-related pain in women with stage IV disease, with no recurrence for six months post-treatment.[13] Amir et al compared letrozole and dienogest in recurrent endometrioma, finding both effective for pain, though dienogest showed superior cyst size reduction.[14]

Metformin, an insulin-sensitizing agent widely used in polycystic ovary syndrome, has demonstrated anti-inflammatory and anti-proliferative effects in endometriosis.[15] It reduces pro-inflammatory cytokines and suppresses aromatase activity in endometriotic stromal cells.[16] It also affects steroidogenesis in granulosa and theca cells, and decreases VEGF and MMP-9 while increasing antioxidant enzymes and MMP-2 in endometrial lesions.[17,18]

Metformin regulates local estrogen production by inhibiting PGE2-induced aromatase expression and CYP19A1, as well as downregulating steroidogenic acute regulatory (StAR) protein expression through AMPK-mediated disruption of the CREB-CRTC2 complex.[19] In a clinical study by Foda et al infertile women with early-stage endometriosis treated with metformin showed significant symptom relief, reduced IL-6, IL-8, VEGF levels, and increased pregnancy rates.[20]

These findings suggest that metformin may offer therapeutic benefits by modulating estrogen synthesis, reducing inflammation, and limiting angiogenesis and tissue invasion. As both letrozole and metformin are cost-effective, ovulation-sparing options, their combination may enhance outcomes in symptomatic endometrioma.

With this background, the present study was conducted to compare the efficacy of letrozole plus metformin versus letrozole alone in the treatment of women with symptomatic endometrioma.

Objectives

Objectives were to evaluate the efficacy of letrozole plus metformin versus letrozole alone in reducing endometrioma size, pain, and serum IL-6 levels, with comparable side effects.

METHODS

This RCT was conducted at the department of reproductive endocrinology and infertility, BSMMU, Dhaka, Bangladesh, from January 2022 to June 2023. A total of 50 women with sonographically diagnosed endometrioma (mean diameter <5 cm) and dysmenorrhea were enrolled and randomized equally into two groups. Group A received letrozole (2.5 mg/day) plus metformin (1500 mg/day), while group B received letrozole alone (2.5 mg/day) for 3 months. Participants were randomized via permuted block randomization, and allocation concealment was done using sequentially numbered sealed opaque envelopes. Pretreatment assessment of endometrioma size was performed by transvaginal ultrasonography. The mean endometrioma diameter (average of the two largest transverse measurements) was recorded. All patients were evaluated for the presence and intensity of pain (dysmenorrhea), which was recorded using the VAS score (VAS: 0=no pain, 10=worst pain), and serum IL-6 levels were measured by chemiluminescence immunoassay. They were called every month to check for compliance or any side effects. Size of endometrioma, pain score, and IL-6 level were recorded prior to treatment and at the end of the 3rd month of treatment. All the data were entered into the data sheet for this study. Statistical analysis was done using SPSS version 23. Continuous variables (mean±SD) were

analyzed with paired/unpaired t-tests; categorical variables (%) with chi-square tests (significance: $p<0.05$). The study was approved by BSMMU's institutional review board. Written informed consent was obtained, with confidentiality maintained through anonymized identifiers.

Inclusion criteria

Women of reproductive age (18-39 years), infertile women, diagnosed case of endometrioma by ultrasound imaging with mean diameter <5 cm and patients presenting with dysmenorrhea awaiting ART or surgical treatment were included.

Exclusion criteria

Contraindication to letrozole or metformin, presence of any medical or surgical comorbidity (pulmonary, cardiac, renal, or hepatic disease), presence of other ovarian cyst types or endometriotic cysts >5 cm and history of hormonal treatment, including contraceptives, within the past 3 months were excluded.

RESULTS

Table 1 shows that mean age was 29.6±5.7 years in group A (Letrozole plus metformin) and 28.0±4.7 years in group B (Letrozole alone). The majority of participants in both groups were housewives. Nearly half of the participants in each group had a household income of ≥30,000 Taka per month. Most participants had primary infertility, accounting for 68.0% in group A and 64.0% in group B. There was no statistically significant difference ($p>0.05$) between 2 groups in any of socio-demographic variables.

Table 1: Socio-demographic characteristics of the study population (n=50).

Variables		Group A (Letrozole + metformin) (n=25)		Group B (Letrozole alone) (n=25)		P value
		N	%	N	%	
Age (in years)	<20	1	4.0	0	0.0	
	20-24	4	16.0	8	32.0	
	25-29	7	28.0	5	20.0	
	30-34	6	24.0	10	40.0	
	35-39	7	28.0	2	8.0	
	Mean±SD	29.6±5.7		28.0±4.7		0.292[ns]
	Range (min-max)	18.0-39.0		20.0-39.0		
Occupational status	Housewife	21	84.0	19	76.0	0.480[ns]
	Service	4	16.0	6	24.0	
Household income (Taka)	<30,000	16	64.0	14	56.0	0.564[ns]
	≥30,000	9	36.0	11	44.0	
Residence	Urban	14	56.0	10	40.0	0.258[ns]
	Rural	11	44.0	15	60.0	
BMI (kg/m²)	<18.5	1	4.0	0	0.0	
	18.5-24.9	12	48.0	14	56.0	
	25.0-29.9	8	32.0	9	36.0	
	≥30.0	4	16.0	2	8.0	
	Mean±SD	24.5±4.3		24.1±3.6		0.761[ns]
	Range (min-max)	18.3-32.8		19.3-31.9		
Infertility	Primary	17	68.0	16	64.0	0.765[ns]
	Secondary	8	32.0	9	36.0	
Duration of infertility (in years)	≤5	12	48.0	14	56.0	0.571[ns]
	>5	13	52.0	11	44.0	
Menstrual cycle	Regular	25	100.0	23	92.0	0.245[ns]
	Irregular	0	0.0	2	8.0	

*NS-P value not statistically significant

In the letrozole plus metformin group, there was a statistically significant reduction in the mean size of the endometrioma after 3 months of treatment (3.90±0.62 cm vs. 3.13±0.99 cm), with a mean difference of 0.738 cm. The mean visual analog score for pain also showed a significant decrease (6.64±1.62 vs. 2.26±1.35), with a mean difference of 4.347. Additionally, the mean serum IL-6 level significantly decreased from 6.79±4.66 pg/mL to 4.87±2.58 pg/mL, with mean difference of 1.194 pg/mL.

In letrozole alone group, mean size of endometrioma significantly decreased after 3 months of treatment (4.20±0.68 cm vs. 3.94±0.72 cm), with a mean difference of 0.287 cm. Mean VAS for pain also showed statistically

significant reduction (6.20±1.63 vs. 2.75±2.11), with a mean difference of 3.458. However, the change in mean serum IL-6 levels (6.58±2.87 pg/mL vs. 6.24±2.54 pg/mL) was not statistically significant (p=0.135).

Table 4 demonstrates that after three months of treatment, the reduction in endometrioma size was statistically significant between the letrozole plus metformin group and the letrozole alone group (p<0.05). However, differences in pain scores assessed by the VAS and serum cytokine levels (IL-6) between the two groups were not statistically significant (p>0.05).

Table 5 shows that the mean reduction over 3 months in the size of endometrioma, pain severity, and serum IL-6 levels was greater in the letrozole plus metformin group compared to the letrozole alone group.

Table 2: Comparison of clinical and biochemical parameters before and after treatment in the letrozole plus metformin group

Parameters	Baseline (n=25), mean±SD	After 3 months treatment (n=23), mean±SD	Mean difference	Effect size	P value
Size of endometrioma (cm)	3.90±0.62	3.13±0.99	0.738	0.88	0.001[s]
Visual analog score for pain	6.64±1.62	2.26±1.35	4.347	4.061	0.001[s]
Serum IL-6 level (pg/ml)	6.79±4.66	4.87±2.58	1.194	0.577	0.011[s]

*S-P value statistically significant.

Table 3: Comparison of clinical and biochemical parameters before and after treatment in letrozole alone group.

Parameters	Baseline (n=25), mean±SD	After 3 months treatment (n=24), mean±SD	Mean difference	Effect size	P value
Size of endometrioma (cm)	4.20±0.68	3.94±0.72	0.287	0.507	0.021[s]
VAS for pain	6.20±1.63	2.75±2.11	3.458	2.346	0.001[s]
Serum IL-6 level (pg/ml)	6.58±2.87	6.24±2.54	0.447	0.315	0.135[ns]

*NS-P value not statistically significant, S-P value statistically significant.

Table 4: Post-treatment comparison of clinical and biochemical parameters between two groups (n=47).

Outcome measure	Group A (n=23), mean±SD	Group B (n=24), mean±SD	Mean difference	Effect size (Cohen's d)	P value
Size of endometrioma (cm)	3.13±0.99	3.94±0.72	-0.8	-0.93	0.003[s]
VAS for pain	2.26±1.35	2.75±2.11	-0.48	-0.27	0.352[ns]
Serum cytokine level (IL-6) (pg/ml)	4.87±2.58	6.24±2.54	-1.37	-0.53	0.074[ns]

*NS-P value not statistically significant, S-P value statistically significant.

Table 5: Mean reduction in clinical and biochemical parameters over 12 weeks in both groups.

Parameters	Group A (Letrozole+metformin), (n=23)	Group B (Letrozole alone), (n=24)
Size of endometrioma (cm)	0.738	0.287
Visual analog score for pain	4.347	3.458
Serum IL-6 level (pg/ml)	1.194	0.447

Table 6: Side effects observed in the study population, (n=47).

Side effects	Group A (Letrozole+metformin), (n=23)		Group B (Letrozole alone), (n=24)		P value
	N	%	N	%	
Nausea or vomiting	3	13.0	0	0.0	0.109[ns]
Spotting	4	17.4	7	29.2	0.341[ns]
Weakness	2	8.7	0	0.0	0.234[ns]
Hot flush	0	0.0	1	4.2	0.511[ns]
Loose motion	1	4.3	0	0.0	0.489[ns]

*NS-P value not statistically significant, S-P value statistically significant.

Table 6 shows that 3 patients (13.0%) in group A (letrozole + metformin) experienced nausea or vomiting, which was not observed in group B (Letrozole alone). Spotting was reported by 4 patients (17.4%) in group A and 7 patients (29.2%) in B. Weakness occurred in 2 patients (8.7%) in group A and was not reported in B. One patient (4.3%) in group A had loose motion, while 1 patient (4.2%) in group B reported hot flushes. None of these differences were statistically significant ($p>0.05$) between 2 groups.

DISCUSSION

The medical management of endometriosis primarily focuses on the suppression of endogenous estrogen production, which is crucial for the growth and maintenance of endometriotic tissue. While several hormonal therapies such as GnRH analogues, oral contraceptives, and progestins have been used, their associated adverse effects, including suppression of ovulation and systemic hypoestrogenism, often limit long-term adherence. In this regard, metformin emerges as a promising therapeutic option due to its well-established safety profile, affordability, and capacity to target several underlying pathogenic processes involved in endometriosis. In addition to its anti-hyperglycemic properties, metformin exhibits anti-proliferative, anti-inflammatory, and anti-estrogenic actions, as evidenced by its capacity to inhibit endometrial stromal cell growth and inflammatory cytokine production.[21]

Similarly, letrozole, a third-generation aromatase inhibitor, has gained attention as a potential treatment for endometrioma due to its targeted suppression of local estrogen synthesis, leading to reduction in lesion size and pain.[22] Considering the potentially synergistic actions of metformin and letrozole, the present study was designed to evaluate and compare the therapeutic efficacy of combined letrozole and metformin treatment versus letrozole monotherapy in managing symptomatic endometrioma.

The demographic profile of study participants revealed that the majority belonged to the age group of 30–34 years, with mean ages of 29.6±5.7 years in the combination group (Group A) and 28.0±4.7 years in the letrozole-only group (Group B). These findings align with previous studies, such as Foda et al who reported a mean age of 27.12±3.48 years in their metformin group.[20] Amir et al also found a mean age of 29.56±4.01 years in their letrozole group, which closely resembles the age distribution in our study.[14] Additionally, the majority of women in both groups resided in urban areas, had regular menstrual cycles, and belonged to higher socioeconomic strata, as indicated by household incomes exceeding 30,000 takas. This demographic pattern may reflect increased awareness and access to healthcare services among urban and economically advantaged women, as well as a potential link between higher socioeconomic status and greater diagnostic opportunities for endometriosis.

In terms of reproductive history, the present study found that more than half (52.0%) of women in the combination group and 44.0% in the letrozole-only group had infertility duration exceeding five years. This observation is consistent with findings by Amir et al who reported a mean infertility duration of 6.17±3.39 years in their letrozole cohort.[14] Primary infertility was more prevalent than secondary infertility in our population, highlighting the significant impact of endometriosis, particularly ovarian endometriomas, on fertility potential.

The average BMI of participants in both groups was within the normal range-24.5±4.3 kg/m² in group A and 24.1±3.6 kg/m^2 in group B. These values are slightly lower than those reported by Foda et al who observed higher BMIs in both their metformin and control groups.[20] However, our results are closely aligned with those of Ansary et al who reported a baseline BMI of 23.5±3 kg/m^2 in their letrozole group.[22] The absence of significant differences in baseline BMI and other clinical or biochemical parameters between groups indicates proper randomization and comparability of the study cohorts.

One of the key findings of this study was the significant reduction in endometrioma size following three months of treatment in both groups, though the magnitude of reduction was more pronounced in the combination group. In group A, the mean cyst diameter decreased from 3.90±0.62 cm to 3.13±0.99 cm, whereas in group B, it decreased from 4.20±0.68 cm to 3.94±0.72 cm. These findings mirror those of Oner et al who found comparable reductions in endometriotic implant size in animal models treated with either metformin or letrozole.[23] Jamali et al also reported marked reductions in implant size with metformin-containing regimens.[24] Our results thus reinforce the therapeutic potential of combined metformin and letrozole treatment for size reduction in ovarian endometriosis.

Pain scores, assessed by the VAS, also showed significant improvement in both groups after three months. In group A, the mean VAS score decreased markedly from 6.64±1.62 to 2.26±1.35. In group B, a similar trend was observed, with scores reducing from 6.20±1.63 to 2.75±2.11. Foda et al also reported a notable decrease in pelvic pain and dysmenorrhea following treatment with metformin.[20] The findings from Amir et al and Madny et al also support the efficacy of letrozole in alleviating endometriosis-associated pain, though a longer treatment duration was used in their studies.[13,14]

The role of inflammation in endometriosis pathophysiology is well established, with elevated cytokines such as IL-6 and IL-8 contributing to lesion persistence and symptom severity. Metformin is known to modulate inflammatory pathways by reducing cytokine secretion from endometrial stromal cells.[25] In our study, the serum IL-6 level significantly declined in group A from 6.79±4.66 to 4.87±2.58, while the decrease in group B was less pronounced. Foda et al also reported a significant post-

treatment reduction in IL-6 levels with metformin therapy, supporting its anti-inflammatory efficacy.[20]

Although both treatment groups demonstrated clinical and biochemical improvements, the mean reduction in endometrioma size and IL-6 levels was significantly greater in the combination group, suggesting a synergistic effect of letrozole and metformin. However, between-group comparisons of VAS scores and IL-6 changes did not reach statistical significance, implying that while the combination may offer enhanced benefits, the incremental improvement over letrozole alone in terms of pain and inflammation might be modest or require a larger sample size to detect.

This study is noteworthy as it is among the first to investigate the effect of letrozole combined with a non-hormonal agent like metformin in the management of endometrioma, targeting both size reduction and symptom relief without affecting ovulation. Unlike other studies that used letrozole in conjunction with hormonal agents, which may suppress ovulation and limit fertility outcomes, our regimen may be more appropriate for women desiring conception.

Regarding safety, both regimens were well tolerated. In group A, adverse effects included nausea or vomiting (13.0%), weakness (8.7%), loose motion (4.3%), and spotting (17.4%). Group B had a higher incidence of spotting (29.2%). While the differences were not statistically significant, the findings are consistent with known side-effect profiles. Previous research indicates that gastrointestinal symptoms are common with metformin, while aromatase inhibitors such as letrozole are associated with relatively mild side effects like hot flashes, arthralgia, and headache.[22,26,27]

Limitations

The study had some limitations: The study was conducted with a small sample size. The study population was recruited from a single selected center in Dhaka city, which limits the external validity of the findings. The present study was conducted over a short period of time.

Trial bias: Selection bias was minimized by random allocation and allocation concealment; however, other types of bias were present, such as:

Performance bias: due to lack of blinding of participants and personnel dispensing the drugs.

Detection bias: due to lack of blinding in outcome assessment.

CONCLUSION

The size of the endometrioma, pain, and IL-6 levels decreased significantly in women with endometriosis receiving either combined therapy (Letrozole plus metformin) or letrozole alone; however, the mean reduction in endometrioma size and IL-6 levels was greater in those receiving metformin in addition to letrozole. Therefore, combined therapy may represent a promising treatment option for endometriosis patients with endometrioma who desire fertility.

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