

Letrozole in Endometriosis: A Observational StudySweety Sinha¹, Ankita², Tejaswita Sinha³, Deepshikha⁴¹Associate Professor, Department of Obstetrics and Gynaecology, Patna Medical College and Hospital²Senior Resident, Department of Obstetrics and Gynaecology, Patna Medical College and Hospital³Junior Resident, Department of Obstetrics and Gynaecology, Patna Medical College and Hospital⁴Junior Resident, Department of Obstetrics and Gynaecology, Patna Medical College Hospital

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Abstract:

Background: This prospective observational study aimed to evaluate the clinical efficacy and safety of a multi-drug regimen—letrozole, oral contraceptive pills (OCPs) and calcium supplementation—for the treatment of endometriosis-associated pelvic pain. A total of 50 reproductive-age women with laparoscopically confirmed endometriosis and a baseline Visual Analogue Scale (VAS) pain score of ≥ 5 were enrolled. Participants were divided into two groups: Group A (n=25) received the combination therapy, and Group B (n=25) received OCPs only for a duration of four months. Both groups demonstrated a statistically significant reduction in pain. However, the decline in dysmenorrhea, dyspareunia, and chronic pelvic pain was significantly more pronounced in the letrozole combination group.

These findings suggest that letrozole in combination with OCPs is a promising and effective adjunct therapy for endometriosis, particularly in cases of severe pain, though larger, randomized controlled trials are essential to establish its long-term role in disease management and recurrence prevention.

Objective: This study aimed to evaluate the clinical efficacy and safety of letrozole, a third-generation aromatase inhibitor, when used in combination with oral contraceptive pills (OCPs), and calcium supplementation, compared with OCPs alone, in reducing endometriosis-associated pelvic pain.

Methods: A prospective observational study was conducted at Patna Medical College And Hospital on 50 reproductive-age women with laparoscopically confirmed endometriosis and a baseline pain score of ≥ 5 on the Visual Analogue Scale (VAS). Group A (n = 25) received letrozole + OCP + calcium carbonate, while Group B (n = 25) received OCP only, for 4 months. Pain severity, gastrointestinal symptoms, hormonal profile, and side effects were assessed.

Results: Both groups showed significant pain reduction after 4 months ($p < 0.05$). However, the decline in dysmenorrhea, dyspareunia, and pelvic pain was more pronounced in the letrozole group. Additional improvement in gastrointestinal symptoms, such as bloating and dyschezia, was reported predominantly in the letrozole group. Side effects were minimal, with irregular bleeding being the most common.

Conclusion: Letrozole in combination with OCPs significantly improves pain relief compared to OCP alone. It is a promising adjunct therapy in endometriosis management. Further large-scale randomized trials are warranted to establish its role in long-term disease control and recurrence prevention.

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Introduction

Endometriosis is a chronic, inflammatory, and estrogen-dependent disorder defined by the presence of functional endometrial-like tissue outside the uterine cavity [9,10]. Affecting approximately 7-10% of reproductive-age women, it represents a significant public health burden, often leading to chronic pelvic pain, painful menstruation (dysmenorrhea), painful intercourse (dyspareunia), and infertility [5]. The disease's pathophysiology is complex, driven by a cycle of inflammation and hormonal stimulation. The ectopic tissue, or lesions, responds to hormonal fluctuations, leading to

bleeding, inflammation, and the formation of scar tissue (adhesions). These processes contribute to the hallmark symptoms and can lead to structural damage to pelvic organs.

Current management strategies for endometriosis are often insufficient. Surgical excision, while effective, carries a high risk of disease recurrence. Medical therapies, such as GnRH analogues, progestins, and combined oral contraceptive pills (OCPs), aim to suppress ovarian function and reduce estrogen levels. However, many of these options have significant side effects or limited efficacy in

certain patient populations [1]. For instance, GnRH analogues induce a hypoestrogenic state that can cause menopausal-like symptoms and bone density loss. OCPs are widely used but may not provide adequate pain relief for all patients, especially those with severe or deeply infiltrative disease.

A major breakthrough in understanding endometriosis was the discovery that the lesions themselves can produce their own estrogen [2]. This is facilitated by the aberrant expression of the enzyme aromatase, which converts androgens into estrogen within the ectopic tissue, creating an auto-sustaining hormonal environment that promotes lesion growth and inflammation. This local estrogen production serves as the rationale for the use of aromatase inhibitors (AIs) [11]. Letrozole, a highly potent third-generation AI, offers a targeted approach by directly blocking this local estrogen synthesis, thereby potentially halting the disease at its source [4]. This study was designed to investigate whether combining letrozole with a standard OCP regimen could provide superior pain control compared to OCPs alone, while also assessing the safety and tolerability of this novel approach.

Epidemiology

- Prevalence in reproductive-age women: 7–10%.
- Prevalence in women with dysmenorrhea: ~60%.
- Prevalence in women with subfertility: ~30%.
- It is also suspected in up to 22% of asymptomatic women diagnosed incidentally during surgery.

Clinical Manifestations

- Dysmenorrhea (painful menstruation).
- Dyspareunia (pain during intercourse).
- Non-cyclic chronic pelvic pain.
- Dyschezia (painful bowel movement).
- Infertility.
- Occasionally, urinary or gastrointestinal symptoms depending on lesion location.

Current Management Approaches

- **Surgical:** Laparoscopic excision/ablation of lesions; effective but recurrence rates are high.
- **Medical:**
 - GnRH analogues: Suppress ovarian function, effective but associated with menopausal side effects.
 - Progestins: Cause decidualization and atrophy of lesions.
 - Danazol: Effective but limited by androgenic side effects.
 - Combined OCPs: Widely used to suppress ovulation and reduce pain.

Letrozole is a third-generation aromatase inhibitor. As there is aberrant aromatase production by

endometriotic stromal cells & the growth and regression of endometriosis is estrogen dependent, the use of letrozole to reduce the size and symptoms of endometriosis/ endometriomas especially in recurrent cases is a promising medical intervention [11].

Rationale for Letrozole Use

- Endometriotic lesions have aberrant aromatase expression, enabling autonomous estrogen production.
- Letrozole is a highly selective, third-generation aromatase inhibitor that blocks estrogen biosynthesis locally.
- By suppressing estradiol within endometriotic tissue, lesion growth and associated pain are reduced.
- Calcium supplementation is added to prevent bone loss caused by hypoestrogenic effects.

Materials and Methods

This was a single-center, prospective observational study conducted over a total duration of six months (October 2024 to March 2025) in Patna Medical College & Hospital at Patna, Bihar, with a four-month treatment period. A total of 50 women between the ages of 18 and 45 were enrolled after history, clinical features and USG findings suggestive of endometriosis with predominant complain of pain [1]. All participants had to have a baseline pelvic pain score of ≥ 5 on the 10-point Visual Analogue Scale (VAS) to qualify.

Inclusion Criteria

- Reproductive-age women (18–45 years).
- Regular, predictable menstrual cycles.
- Endometriosis confirmed by diagnostic laparoscopy.
- Persistent or recurrent pelvic pain despite conservative laparoscopic surgery.
- Dysmenorrhea or pelvic pain for ≥ 2 weeks in the past 3 months.

Exclusion Criteria

- Unexplained vaginal bleeding.
- Ovarian endometriomas >2 cm.
- Hypersensitivity to letrozole.
- Pregnancy or lactation.
- Medical contraindications: severe pulmonary, cardiac, renal, hepatic disease, seizure disorder.

Participants were assigned to one of two treatment arms:

- Group A (Combination Therapy; n=25): Patients received a daily dose of letrozole (2.5 mg), calcium carbonate (1000 mg), and a standard daily combined oral contraceptive pill. The OCP was included to prevent ovarian cyst formation, a known side effect of AIs. Calcium

supplementation was provided to mitigate the risk of bone mineral density loss associated with reduced estrogen exposure

- **Group B (OCP Monotherapy; n=25):** Patients received a daily standard combined oral contraceptive pill alone, consistent with current best practice guidelines for pain management.
- Pain severity was assessed at baseline and at the end of the four-month treatment period using the VAS. Participants also maintained a daily patient diary to record pain levels, bleeding patterns, and any side effects. Additional assessments included monthly safety monitoring of complete blood count (CBC) and liver and renal function tests. Pelvic ultrasounds were performed at baseline and at three and six months to monitor for changes in lesion size. The primary outcome was a statistically significant reduction in VAS scores for dysmenorrhea, dyspareunia, and chronic pelvic pain. Secondary outcomes included improvement in gastrointestinal symptoms and overall safety and tolerability of the treatment regimen

Treatment Protocol

- **Group A (n = 25):**
 - Letrozole 2.5 mg/day.
 - Calcium carbonate 1000 mg/day.
 - Combined OCP daily.
- **Group B (n = 25):**
 - Combined OCP only.

Assessments

1. Pain severity: Measured using VAS scale (0 = no pain; 10 = worst pain ever experienced).
2. Hormonal profile: LH, FSH, estradiol, and testosterone levels at baseline and post-treatment.
3. Imaging: Pelvic ultrasound at baseline, 3 months, and 6 months.

4. USG: - evidence of endometriotic cyst or other signs of endometriosis.
5. Safety monitoring: CBC, renal, and hepatic function tests monthly.
6. Patient diary: Daily recording of pain, menstrual pattern, bleeding, and any side effects.

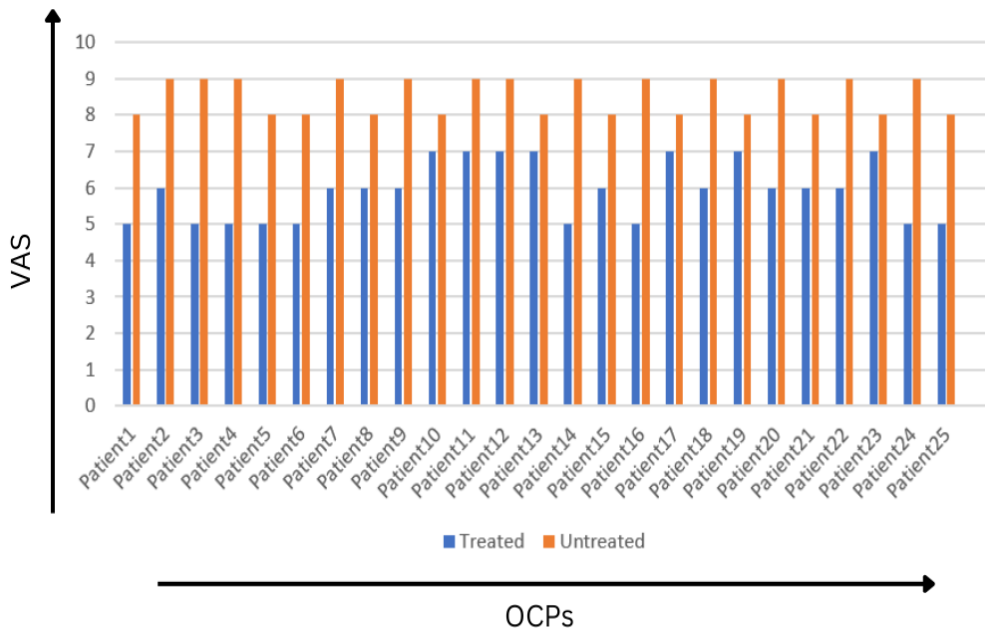
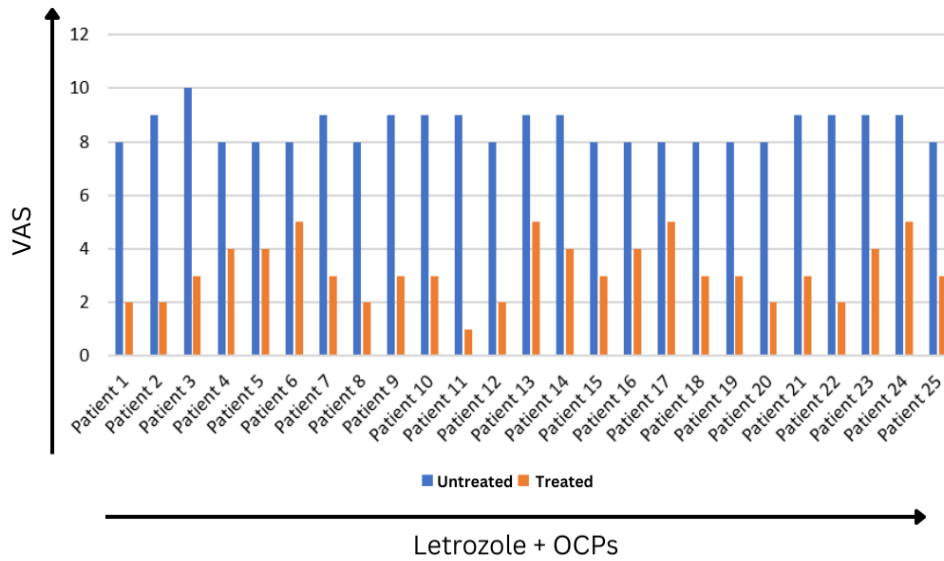
Outcome Measures

- **Primary outcome:** Reduction in VAS scores for dysmenorrhea, dyspareunia, and chronic pelvic pain.
- **Secondary outcomes:**
 - Improvement in gastrointestinal symptoms (bloating, dyschezia).
 - Changes in hormonal profile.
 - Safety/tolerability (side effects, bleeding irregularities, bone health).
 - Change in ASRM laparoscopic staging.

Results

At the conclusion of the four-month treatment period, both Group A and Group B demonstrated a statistically significant reduction in their mean VAS pain scores ($p < 0.05$) [7]. However, a detailed analysis revealed a more profound and clinically meaningful improvement in Group A. The mean VAS scores for dysmenorrhea, dyspareunia, and non-menstrual chronic pelvic pain showed a greater percentage decline in the letrozole combination group compared to the OCP-only group.

A notable secondary finding was the improvement in gastrointestinal symptoms. Of the patients in Group A who reported significant pre-treatment bloating, intestinal cramping, or painful bowel movements (dyschezia), four out of six reported a complete resolution of these symptoms. In contrast, only a minority of patients in Group B reported partial improvement in these symptoms. This suggests that the local estrogen-reducing effect of letrozole may be particularly effective in addressing deeply infiltrative endometriosis affecting the bowel [6, 7].



Systemic hormonal assessments showed no significant changes in circulating estradiol, LH, or FSH levels in either group, indicating that the therapeutic effect of letrozole was likely localized to the endometriotic tissue and did not cause systemic hypoestrogenism. The treatment regimen in Group A was well-tolerated. The most common adverse event in both groups was irregular vaginal bleeding, which was managed with patient counseling and did not lead to treatment discontinuation. No patients in either group discontinued the study due to other adverse events, and a four-month duration was found to be sufficient to preserve bone mineral density.

Discussion

The results of this study provide compelling evidence that adding an aromatase inhibitor like

letrozole to a standard OCP regimen significantly enhances pain relief for women with endometriosis. This finding aligns with the growing understanding of endometriosis as a disease driven by localized estrogen production [2]. The ability of endometriotic cells to produce their own estrogen makes them relatively resistant to therapies that only suppress ovarian function. By directly targeting the aromatase enzyme within the lesions, letrozole effectively starves the tissue of its hormonal fuel, leading to regression and a reduction in inflammation and pain [3, 4].

This study's findings are consistent with previous smaller studies and case reports that have explored the use of aromatase inhibitors in endometriosis. For instance, studies by Amsterdam et al. (2005) [8] and Ferrero et al. (2009) [2] have shown similar benefits with aromatase inhibitors for deeply infiltrative

rectovaginal endometriosis. The combination of letrozole with a progestin (norethindrone acetate) provides a dual mechanism of action: letrozole blocks estrogenic synthesis while norethindrone promotes apoptosis (programmed cell death) and decidualization of the lesions. The inclusion of OCPs in the regimen not only manages bleeding and prevents ovarian cyst formation but also provides a synergistic hormonal suppression [5].

While the results are encouraging, the study has several limitations, most notably its small sample size and observational, non-randomized design. The short four-month treatment duration is also a limitation, as endometriosis is a chronic disease requiring long-term management. These factors limit the generalizability of the findings and the ability to draw definitive conclusions about long-term efficacy and recurrence rates. Future research should include larger, multi-center, randomized controlled trials to validate these findings [7]. Long-term studies are also crucial to assess the sustained effects on pain, recurrence prevention, and fertility outcomes.

Conclusion

Oral contraceptive pills and the combination of OCPs with letrozole are both effective in reducing endometriosis-related pain. However, the addition of letrozole provides a significantly greater improvement in pain outcomes, especially for dysmenorrhea, dyspareunia, and chronic pelvic pain. The regimen is safe and well-tolerated, with minimal side effects that are easily managed. Letrozole presents a promising role as an adjunct therapy, particularly for patients with severe pain or those who have not responded to conventional hormonal treatments. This study lays the groundwork for further research to establish letrozole's long-term utility in the comprehensive management of endometriosis.

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