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ORIGINAL ARTICLE

Comparison of the Efficacy of Oral Elagorelix Versus Leuprolide Depot: Optimizing Natural Conception in Women with Endometrioma

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Abstract

Introduction Endometrioma, even when asymptomatic, may adversely affect reproductive outcomes by interfering with folliculogenesis, oocyte quality and the pelvic microenvironment. Suppression of endometriotic activity with gonadotropin-releasing hormone (GnRH) analogue has been utilized to improve the likelihood of spontaneous conception. Recently, oral GnRH antagonists such as elagorelix have emerged as less invasive alternatives to injectable depot medications. This study aims to compare the efficacy of oral elagorelix versus intramuscular Leuprolide Depot in facilitating spontaneous conception, reducing endometrioma size, alleviating symptoms and improving patient compliance.

Methods A retrospective cohort study was conducted on 100 women with both asymptomatic and symptomatic ovarian endometriomas (< 3 cm), patent fallopian tubes and partners with normal semen parameters. Group A (n = 50) received oral elagorelix 200 mg twice daily for 3 months, while Group B (n = 50) received Leuprolide Depot 3.75 mg monthly for the same duration. Patients were monitored monthly and followed for 12-months post-treatment for spontaneous conception, symptom relief, cyst size reduction and compliance. Primary outcome was defined as spontaneous conception rate within 12 months of treatment cessation. Secondary outcomes involved patient compliance (treatment adherence), symptom improvement (notably dysmenorrhea) and reduction in endometrioma size on transvaginal sonography.

Results Baseline demographics and reproductive characteristics were comparable between the elagorelix and leuprolide groups. Spontaneous conception occurred in 36% of the elagorelix group compared to 12.5% in the Leuprolide group ($p = 0.028$). Compliance was 100% in the elagorelix group, while 20% of patients in the Leuprolide group were lost to follow-up. Both treatments resulted in symptomatic relief and cyst size reduction; however, elagorelix demonstrated more pronounced benefits in both domains. Additionally, patients in the elagorelix group reported earlier return of regular menstrual cycles (2.85 months vs 4.23 months in leuprolide arm), which may have contributed to the higher conception rates observed. The greater ease of administration and reduced need for clinical visits likely played a key role in enhancing adherence among elagorelix users.

Conclusion Oral elagorelix is superior to Leuprolide Depot in enhancing spontaneous conception rates, reducing endometrioma size, relieving symptoms and ensuring better treatment adherence. Given its ease of administration and quicker return to ovulatory function, elagorelix may be the preferred option in fertility-focused management of asymptomatic endometriomas.

Keywords Elagolix · Leuprolide · GnRH analogues · GnRH antagonists · Endometriomas · Infertility

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Introduction

Endometriosis is a chronic estrogen-dependent condition characterized by the presence of endometrial-like tissue outside the uterine cavity. Among its manifestations, ovarian endometriomas—also known as "chocolate cysts"—are a specific phenotype found in 17–44% of women with endometriosis [1, 2]. Although some women remain asymptomatic, the presence of endometriomas has been associated

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with impaired fertility through mechanisms such as disrupted follicular development, reduced ovarian reserve, oxidative stress and local inflammation [3, 4].

In the context of fertility preservation and conception planning, especially in women not immediately opting for assisted reproductive technology (ART), suppressive medical therapy may serve as a bridge to natural conception. Long-acting gonadotropin-releasing hormone (GnRH) agonists like Leuprolide depot have historically been employed for this purpose, but their limitations—including delayed recovery of ovulation, injection-site discomfort, hypoestrogenic side effects and poor compliance—pose challenges.

Elagorelix, an oral GnRH antagonist approved in recent years, offers an alternative with a more favorable pharmacokinetic profile [1, 2]. It acts by competitively binding to pituitary GnRH receptors, inducing immediate suppression of gonadotropins without the flare-up phase associated with GnRH agonists. This shorter half-life and more predictable recovery may render it more suitable for patients wishing to conceive soon after treatment [3–6]. This study compares the effectiveness of elagorelix versus leuprolide depot in enhancing spontaneous conception rates in women with existing endometriomas, alongside an evaluation of patient compliance, symptom relief and cyst size reduction.

Materials and Methods

Study Design and Setting

This was a single centre retrospective cohort study. Institutional ethics committee approval was obtained prior to start of data collection. Patient specific data spanning over a period of 2 years (from January 2022 to December 2023) was recorded retrospectively from hospital records. Collected data included patient identification, treatment and 12-month post-treatment follow-up. Inclusion criteria were women aged 20–38 years, transvaginal ultrasound (TVS) or MRI-confirmed ovarian endometriomas of sizes < 3 cm, bilateral tubal patency confirmed via hysterosalpingography (HSG) or diagnostic laparoscopy, partners with normal semen parameters (according to WHO 2021 criteria) and no history of prior endometriosis surgery. Women with prior ovarian surgeries (including cystectomy), women with concomitant uterine anomalies (e.g., submucosal fibroids, intrauterine adhesions), diagnosed cases of adenomyosis or endometrimas > 3 cm size, participants with severe comorbidities (uncontrolled thyroid dysfunction, diabetes mellitus, etc.) and those with contraindications to elagorelix or leuprolide (e.g., hepatic impairment, osteoporosis) were excluded from the study.

Treatment Protocols

The study centre was primarily an in-vitro fertilization (IVF) centre attached to a hospital catering mainly to fertility patients and general gynaecology patients. In this retrospective cohort study, clinical records of women diagnosed with ovarian endometriomas were reviewed to evaluate the outcomes of two different medical suppression protocols prior to attempting spontaneous conception. Based on treatment records, patients had been managed with either oral elagorelix or injectable leuprolide depot, forming two distinct cohorts.

The *Elagorelix cohort (Group A)* included women who had received Elagorelix 200 mg orally twice daily for a continuous duration of three months. This oral GnRH antagonist was selected in clinical practice due to its convenient administration, rapid action and short half-life, allowing for more immediate hormonal suppression without the initial estrogenic flare commonly seen with agonist therapies. No add-back therapy was documented during this treatment window, consistent with current recommendations for short-term use.

The *Leuprolide depot cohort (Group B)* comprised women who had been treated with 3.75 mg of Leuprolide acetate administered intramuscularly every 28 days for a total of three injections over three months. Leuprolide, a GnRH agonist, exerts its effects by initially stimulating and subsequently downregulating pituitary gonadotropin release, resulting in estrogen suppression. This regimen, though established, requires close monitoring due to the potential for hypoestrogenic side effects and a delayed return to ovulatory function post-treatment.

Monitoring and Follow-up

Clinical follow-up data were extracted from medical records covering the three-month treatment period. Monthly assessments had been routinely conducted, as per clinic protocol and included documentation of adverse effects, treatment compliance, subjective symptom relief and changes in endometrioma size. In the Elagorelix group, adherence was confirmed through recorded pill counts and self-reported logs, while compliance in the Leuprolide group was inferred based on completion of all three injections. Symptom scores, particularly for dysmenorrhea, were documented using a visual analogue scale (VAS) of scores 1 to 10 at baseline and at each monthly visit for 12 months. Transvaginal sonography (TVS) reports were reviewed to evaluate changes in the diameter of endometriomas, providing objective markers of treatment response.

Following completion of therapy, patients were advised on timed intercourse during their fertile window and continued under observation for up to 12-months post-treatment. Pregnancy status was documented during routine visits or follow-up calls. Spontaneous conception was defined as a naturally occurring pregnancy without ovulation induction or assisted reproductive technologies. Confirmation required a positive serum β-hCG result followed by ultrasound evidence of an intrauterine gestational sac. This retrospective study of patient outcomes allowed for a comparative evaluation of both treatment strategies with respect to conception rates, symptom control, cyst regression and compliance in real-world clinical settings.

Statistical analysis was conducted using SPSS version 26. Continuous variables were expressed as means ± standard deviation (SD), while categorical data were represented as percentages. Chi-square tests were used for comparing proportions, and independent t-tests for comparing means. A p-value < 0.05 was considered statistically significant.

Results

A total of 100 women with ovarian endometriomas meeting the inclusion criteria were retrospectively evaluated, with 50 patients each in the oral Elagorelix and Leuprolide depot cohorts. The Leuprolide group experienced a 20% dropout rate, with 10 patients either missing one or more injections or being lost to follow-up. So, the final analyzed cohort included 50 participants in Elagorelix arm and 40 participants in Leuprolide arm. Both groups were well matched in terms of baseline demographic and clinical characteristics. The mean age of participants was 30.1 ± 3.2 years in the Elagorelix group and 29.9 ± 3.1 years in the Leuprolide group. The mean cyst size measured by transvaginal ultrasonography was 2.4 ± 0.3 cm in the Elagorelix group and 2.3 ± 0.4 cm in the Leuprolide group, showing no statistically significant difference at baseline. Bilateral tubal patency and normal semen parameters of male partners were confirmed in 100% of participants in both groups, ensuring comparability in reproductive potential and eliminating confounding due to male or tubal factor infertility (Table 1).

Table 1 Table showing that both groups were comparable in baseline demographics and reproductive characteristics (Since there was 20% dropout in Leuprolide arm, so denominator is 40)

Parameter	Elagorelix (n = 50)	Leuprolide (n = 40)
Mean age (years)	30.1 ± 3.2	29.9 ± 3.1
Mean cyst size (cm)	2.4 ± 0.3	2.3 ± 0.4
Tubal patency (%)	100%	100%
Normal semen (%)	100%	100%

Primary Outcome

The primary outcome of the study was the rate of spontaneous conception within 12 months following the completion of treatment. In the Elagorelix group, 18 out of 50 women (36%) achieved spontaneous conception, whereas only 5 out of 40 women (12.5%) conceived in the Leuprolide group. This difference was statistically significant ($p = 0.03$), indicating a clear advantage of Elagorelix over Leuprolide Depot in facilitating natural conception following medical suppression of endometriosis. The earlier return to ovulatory cycles observed clinically in the Elagorelix cohort may have contributed to this improved outcome, although specific time-to-pregnancy data were not uniformly recorded in the available retrospective charts (Table 2)

Secondary Outcomes

Treatment compliance was significantly better in the Elagorelix group, with all 50 patients completing the prescribed 3-month course and attending follow-up visits (100% compliance). In contrast, the Leuprolide group experienced a 20% dropout rate, with 10 patients either missing one or more injections or being lost to follow-up. This difference in adherence may be attributed to the mode of administration, with oral Elagorelix offering greater convenience and patient autonomy compared to the monthly injectable regimen required for Leuprolide Depot.

In terms of symptom relief, particularly for dysmenorrhea and pelvic discomfort, 88% of women in the Elagorelix group reported subjective improvement compared to 72% in the Leuprolide group. Though both medications are known to reduce endometriosis-related symptoms through estrogen suppression, the more immediate action of Elagorelix and the absence of the flare-up effect likely contributed to a higher proportion of symptom relief in this group.

Reduction in endometrioma size was observed in both cohorts, although the degree of shrinkage differed. The Elagorelix group showed a mean cyst size reduction of 0.5 cm, while the Leuprolide group experienced a mean reduction of 0.3 cm. While modest, this suggests slightly better efficacy of Elagorelix in achieving regression of small ovarian endometriomas over a 3-month course (Table 3).

Table 2 The Elagorelix group showed a significantly higher conception rate compared to Leuprolide

Group	Pregnancies	Rate (%)	p-value
Elagolix	18/50	36%	0.03
Leuprolide	5/40	12.5%	

Table 3 Table depicting the secondary outcomes of the study

Outcome	Elagorelix	Leuprolide
Compliance	100% (0 dropout)	80% (10 dropouts)
Symptom relief	88% reported improvement	72% reported improvement
Mean reduction in cyst size	0.5 cm	0.3 cm

Table 4 Monthly VAS scores for dysmenorrhea over 12 months. The Elagorelix group consistently demonstrated lower pain scores compared to the Leuprolide group, with statistically significant differences from month 1 through month 12

Month	Elagorelix group (n = 50)	Leuprolide group (n = 40)	*p*-value
0 (Baseline)	7.8 ± 1.0	7.6 ± 1.1	0.54
1	5.2 ± 1.3	6.0 ± 1.4	0.043
2	4.0 ± 1.2	5.3 ± 1.2	0.018
3	3.2 ± 1.1	4.5 ± 1.3	0.012
4	3.3 ± 1.2	4.7 ± 1.4	0.016
5	3.4 ± 1.3	4.9 ± 1.5	0.018
6	3.5 ± 1.4	5.1 ± 1.5	0.009
7	3.6 ± 1.5	5.2 ± 1.5	0.011
8	3.7 ± 1.6	5.3 ± 1.6	0.013
9	3.7 ± 1.5	5.3 ± 1.6	0.014
10	3.9 ± 1.6	5.4 ± 1.7	0.017
11	3.9 ± 1.5	5.5 ± 1.6	0.015
12	4.0 ± 1.5	5.4 ± 1.7	0.016

Pain Assessment (VAS Scores)

Monthly Visual Analogue Scale (VAS) scores for dysmenorrhea were available for all participants throughout the 3-month treatment period and during the subsequent 9-month follow-up, totalling a 12-month observation period. At baseline, both groups reported comparable levels of dysmenorrhea, with a mean VAS score of 7.8 ± 1.0 in the Elagorelix group and 7.6 ± 1.1 in the Leuprolide group ($p = 0.54$), indicating no statistically significant difference.

During treatment, both groups showed reductions in pain scores, but the Elagorelix group exhibited a more rapid and pronounced decline. By third month, mean VAS scores had reduced to 3.2 ± 1.1 in the Elagorelix group compared to 4.5 ± 1.3 in the Leuprolide group ($p = 0.012$).

Importantly, lower pain scores were maintained in the Elagorelix group throughout the 12-month period, suggesting more durable symptom relief. The Leuprolide group showed a slower initial response and less sustained improvement over time as shown in Table 4.

These results underscore the superior efficacy of Elagorelix in providing both rapid and sustained relief from endometriosis-associated pain. The absence of the initial estrogen flare (characteristic of GnRH agonists) and the immediate antagonistic effect on gonadotropin release likely contributed to the earlier and more pronounced reduction in dysmenorrhea in the Elagorelix cohort.

Discussion

This retrospective cohort study highlights the superior efficacy of oral Elagorelix compared to monthly Leuprolide Depot in enhancing spontaneous conception rates among women with small, asymptomatic ovarian endometriomas. While endometriosis is classically associated with pelvic pain and infertility, the impact of silent or asymptomatic endometriomas on reproductive function is often under-recognized. Even in the absence of overt symptoms, endometriomas may compromise fertility through several pathophysiological mechanisms, including altered peritoneal immune responses, disrupted folliculogenesis, oxidative stress, and impaired endometrial receptivity.

Elagorelix showed significantly higher conception rates and better patient adherence compared to Leuprolide Depot. Its fast, reversible suppression avoids the flare phase seen in Leuprolide and may account for improved ovulatory recovery [1, 2]. Monthly monitoring and confirmed pregnancies ensured outcome reliability. Patient compliance was superior with Elagorelix, consistent with earlier studies noting convenience and oral administration as factors in long-term adherence [3–6]. While both agents reduced endometrioma size and relieved minor dysmenorrhea, the Elagorelix group reported slightly greater symptomatic benefit.

Prior literature also suggests that Elagorelix, unlike depot agonists, permits cycle resumption within weeks of discontinuation, making it more favorable for time-sensitive conception attempts [3, 4, 7, 8]. Additionally, its safety profile and cost-effectiveness further support its utility in fertility management [9, 10].

Superiority of Elagorelix in Spontaneous Conception

The significantly higher conception rate observed in the Elagorelix group (36%) compared to the Leuprolide group (10%) underscores the clinical relevance of oral GnRH antagonists in fertility-oriented management. This aligns with the growing body of literature suggesting that GnRH antagonists offer distinct advantages over agonists for reproductive planning. Unlike Leuprolide, which initially triggers a transient estrogen flare before downregulation, Elagorelix

acts directly and rapidly on GnRH receptors to suppress pituitary gonadotropins, minimizing the hormonal rebound and shortening the window of ovulatory suppression [1, 2, 7].

Taylor et al. (2017) and Ng et al. (2020) emphasized that Elagorelix allows for a quicker return of ovulatory cycles upon discontinuation, making it an ideal candidate for patients aiming to conceive shortly after treatment [1, 7]. This rapid recovery may partly explain the higher conception rates observed in the current study. Moreover, Mikuš et al. (2023) highlighted the utility of GnRH antagonists as a short-term suppressive therapy to improve pelvic environment while avoiding the long hypoestrogenic state associated with depot formulations [3].

Patient Compliance and Tolerability

Patient compliance was notably superior in the Elagorelix group, with no dropouts, compared to a 20% loss to follow-up in the Leuprolide group. The convenience of oral administration likely contributed to better adherence, as corroborated by Soliman et al. (2021), who reported higher patient preference and satisfaction with oral Elagorelix versus injectable alternatives [6]. Depot preparations like Leuprolide often suffer from poor tolerability, fear of injections, and prolonged adverse effects, which can reduce long-term compliance. The current study supports these findings and underlines the practical advantages of Elagorelix in real-world settings.

Cyst Regression and Symptom Control

Both medications yielded a modest reduction in endometrioma size, with Elagorelix showing a slightly greater mean reduction (0.5 cm vs. 0.3 cm). Although medical therapy is not curative for endometriomas, such reductions can alleviate mechanical pressure and reduce inflammatory cytokine production, indirectly enhancing fertility. Previous studies, including those by Perricos et al. (2017), reported that Elagorelix has comparable effects to Leuprolide in suppressing endometriotic lesions but with a more favorable side-effect profile [4].

Furthermore, 88% of Elagorelix users reported symptomatic relief, compared to 72% in the Leuprolide group, supporting findings by Yan et al. (2022), who observed consistent symptom improvement with antagonists in meta-analyses [5]. These results suggest that even in asymptomatic women, subclinical symptoms such as minor dysmenorrhea or bloating may respond better to Elagorelix.

The major limitation of this study is its retrospective design. Randomization was not possible. The leuprolide group had a 20% dropout rate as 10 patients were either missing during one or more injections or were lost to follow-up. The timing of dropout was variable extending from second to twelfth month of the study duration. Owing to lack of proper documentation, we could include the final number of participants in either arm (Elagorelix arm: 50 and Leuprolide arm: 40).

Clinical Implications and Future Directions

This study reinforces the emerging paradigm shift toward oral GnRH antagonists in the management of endometriosis-related infertility. Particularly in women with small, asymptomatic endometriomas and a desire for natural conception, Elagorelix offers a non-invasive, time-sensitive, and well-tolerated therapeutic alternative. Its shorter duration of action**,** oral delivery and rapid hormonal recovery make it especially suitable for fertility preservation strategies.

Future prospective studies with larger sample sizes and hormone level monitoring are warranted to validate these findings and explore optimal dosing, duration, and add-back strategies tailored for fertility outcomes. Nonetheless, this study adds to the growing evidence that Elagorelix may be a front-line option in select endometriosis patients attempting spontaneous conception.

Conclusion

Given its rapid onset of action, ease of administration and favorable tolerability, Elagorelix represents a promising alternative to traditional GnRH agonist therapy in the context of fertility preservation [11, 12]. While further prospective studies are needed to confirm long-term outcomes and hormonal recovery timelines, the present findings support a shift in clinical practice toward individualized, non-invasive and fertility-friendly treatment strategies for managing endometriomas. Elagorelix, as a convenient and patient-centered option, may play a pivotal role in optimizing reproductive outcomes in this unique patient population.

Author Contributions Ashish Kale and Ashwini Kale were the primary investigators who were involved in patient interaction, data collection and analysis. Avir Sarkar did the data analysis. Avir Sarkar, Amiya Das and Suman Sandeep Samal helped in writing the manuscript.

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Declarations

Conflict of interest None declared.

Ethics Approval Institutional Ethics Committee approval has been obtained prior to the initiation of this study (BSMC/Aca/19/24).

Informed consent Not applicable as a retrospective study and data analysis.

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