



Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.journals.elsevier.com/european-journal-of-obstetrics-and-gynecology-and-reproductive-biology

Full length article

Expert opinion by Federation of Obstetric and Gynaecological Societies of India on elagolix – Redefining the endometriosis therapy landscape

Sunita Tandulwadkar^{a,*}, Basab Mukherjee^b, Chaitanya Ganpule^c, Madhuri Patel^d, Subash Mallya^e, P.M. Gopinath^f, Brajbala Tiwari^g

^a Ruby Hall Clinic / Ruby Hall IVF & Endoscopy Centre, Pune, India^b Aashirbad Clinic, Kolkata, India^c Yash IVF Deccan/ Yash IVF Hadapsar/ Yash IVF Satara, Pune, India^d Disha Clinic, Mumbai, India^e Baby Memorial Hospital & PVS Hospital, Calicut, India^f Reproductive Medicine Kauvery Hospital, Chennai, India^g Life Care Hospital Ltd, Vijay Nagar, India

ARTICLE INFO

Keywords:

Endometriosis
Gonadotrophin-releasing hormone antagonist
Dysmenorrhoea
Non-menstrual pelvic pain
Dyspareunia
Elagolix

ABSTRACT

Background: Endometriosis is a substantial public health challenge, affecting nearly 10% of women of reproductive age. Given the therapeutic benefits of elagolix over conventional therapies, along with the growing body of clinical evidence, a comprehensive evaluation of its role in managing endometriosis is warranted.

Methods: An expert panel meeting was convened to deliberate on the clinical positioning of elagolix in the management of endometriosis-associated pain and to develop a comprehensive guideline on using elagolix in endometriosis. A literature search was conducted using the PubMed and Google Scholar databases to evaluate the efficacy and safety of elagolix in endometriosis-associated pain.

Results: In pivotal clinical trials, elagolix demonstrated a significant reduction in dysmenorrhoea and non-menstrual pelvic pain among women with endometriosis. Beyond pain relief, elagolix was associated with marked improvements in dyspareunia, fatigue and health-related quality of life. The safety profile of elagolix was favourable, with the most commonly reported adverse events being hot flushes, headache and nausea. When compared with current therapies, elagolix showed comparable efficacy with fewer hypo-oestrogenic side effects, such as bone mineral density loss, breakthrough bleeding and mood disturbances.

Conclusion: Elagolix provides dose-dependent oestrogen suppression and significant pain relief in all types of endometriosis pain, including dyspareunia. Elagolix also provides notable improvements in quality of life with a more favourable safety profile compared to conventional therapies. These attributes position elagolix as an emerging first-line treatment option for the management of endometriosis-associated pain.

Introduction

Endometriosis is a benign, chronic disease that affects approximately 10% of women of reproductive age [1,2]. Nearly 42 million women in India are afflicted by endometriosis [1]. Endometriosis can cause various symptoms, predominantly pain, manifesting as dysmenorrhoea, deep dyspareunia and non-menstrual chronic pelvic pain (NMPP), and can significantly affect quality of life (QoL) [2–4].

The medical management of endometriosis focuses on reducing pain and suppressing hormonally active endometriotic tissue [5]. Currently available treatments for endometriosis-associated pain (EAP), as

recommended by the 2022 European Society of Human Reproduction and Embryology (ESHRE) guideline and 2024 Federation of Obstetric and Gynaecological Societies of India (FOGSI) Good Clinical Practice Recommendations (GCPR), include non-hormonal therapies such as non-steroidal anti-inflammatory drugs (NSAIDs) and hormonal therapies such as oral contraceptives, progestins, gonadotrophin-releasing hormone (GnRH) agonists and GnRH antagonists [6,7].

With progestin treatment, side effects such as breakthrough bleeding, acne, mood changes, bloating and fluid retention have been observed [8]. Additionally, nearly one-third of women with symptomatic endometriosis do not respond to progestins or low-dose oral

* Corresponding author.

E-mail address: drsunitatandulwadkarmumbai@gmail.com (S. Tandulwadkar).<https://doi.org/10.1016/j.ejogrb.2026.115115>

Received 4 March 2026; Received in revised form 27 March 2026; Accepted 8 April 2026

Available online 9 April 2026

0301-2115/© 2026 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

contraceptives due to progesterone resistance [9]. GnRH agonists have been associated with loss of bone mineral density (BMD) and an initial flare-up effect [10,11].

According to the oestrogen threshold hypothesis, lowering oestrogen levels so that they lie within the therapeutic window corresponding to E2 concentrations of 30 to 45 pg/mL can help prevent the growth of endometriotic lesions while preventing hypo-oestrogenic effects such as bone loss [12]. GnRH antagonists are effective as they produce dose-dependent suppression of the hypothalamic–pituitary–gonadal axis by competitively binding to GnRH receptors [13]. This results in fewer hypo-oestrogenic effects compared to GnRH agonists, while maintaining treatment efficacy [11].

Elagolix is an orally administered, non-peptide, small-molecule, short-acting competitive GnRH antagonist [13,14]. It was approved by the United States Food and Drug Administration (USFDA) [15] and Health Canada in 2018 [16], and more recently approved by health authorities in Israel [17] and India [18], for the treatment of moderate or severe EAP. Elagolix is effective in relieving EAP and improving health-related quality of life (HRQoL) in affected women [19,20]. The current article provides a comprehensive overview of the evidence and practice-based insights on elagolix to understand its potential as an emerging first-line treatment option for EAP.

Methodology

A structured expert panel meeting was convened in August 2025 to discuss the current evidence and clinical experience, and to develop an expert opinion on the clinical positioning of elagolix. The panel comprised 20 gynaecologists from different regions across India. Relevant data were collated through a comprehensive literature search using PubMed and Google Scholar. The articles were screened using relevant terms such as ‘endometriosis’, ‘elagolix’, ‘GnRH antagonists’, ‘dysmenorrhoea’ and ‘non-menstrual pelvic pain’. Peer-reviewed research articles, reviews, meta-analyses and government publications were considered to ensure a robust synthesis of evidence to guide expert deliberations. The efficacy and safety of elagolix in EAP and potential applications in other clinical indications were discussed, and the experts provided their practice-based insights.

Clinical effectiveness of elagolix in endometriosis

The Elaris Endometriosis (EM)-I, –II, –III and –IV were phase III randomised clinical trials that evaluated the efficacy and safety of elagolix in EAP. The EM-I and EM-II landmark trials were similar trials conducted over 6 months, while EM-III and EM-IV were 6-month extension trials of EM-I and EM-II, respectively [20,21]. The EM-I and EM-II enrolled premenopausal women with a surgically confirmed diagnosis of endometriosis within the previous 10 years, who were experiencing moderate or severe EAP [20,21].

A similar study was conducted in India; however, it used an active comparator, dienogest, making this phase III trial the first of its kind. This active controlled trial included 230 premenopausal female patients with documented endometriosis who were treated with 150 mg elagolix for 24 weeks [22].

Clinical response in dysmenorrhoea and NMPP

At 3 months, in EM-I and EM-II trials, a higher percentage of women demonstrated a clinically meaningful decrease in dysmenorrhoea and NMPP along with a reduced or stable use of rescue analgesics with elagolix at doses of 150 mg once daily (OD) and 200 mg twice daily (BID) compared to placebo (EM-I: $p < 0.001$ for all comparisons; EM-II: $p < 0.001$ for all comparisons except NMPP, where $p = 0.003$ for 150 mg and $p < 0.001$ for 200 mg) (Table 1). These findings were validated by pain scores measured using the Numeric Rating Scale (NRS) at 3 months. The improvements in dysmenorrhoea and NMPP observed at 3 months

Table 1
Improvement in endometriosis-related pain with elagolix at 3 months from EM-I and II trials.

	Percentage of women with a clinically meaningful reduction in dysmenorrhoea	
	150 mg OD	200 mg BID
Results after 3 months		
EM-I	46.4%	75.8%
EM-II	43.4%	72.4%
Results after 12 months		
EM-III	52.1%	78.2%
EM-IV	50.8%	75.9%
Percentage of women with a clinically meaningful reduction in NMPP		
Results after 3 months		
EM-I	50.4%	54.5%
EM-II	49.8%	57.8%
Results after 12 months		
EM-III	67.5%	69.1%
EM-IV	66.4%	67.2%

EM: Elaris Endometriosis; NMPP: Non-menstrual chronic pelvic pain; OD: Once daily; BID: Twice daily.

were sustained over 6 months. Pain reduction with both doses of elagolix was observed within the first treatment cycle in dysmenorrhoea, NMPP and dyspareunia [20].

A first-in-the-world active-controlled phase III study reported that elagolix was non-inferior to dienogest in reducing the NRS score for pain from baseline to Day 85. For elagolix, the mean reduction in NRS scores was -2.43 ± 1.28 at Day 85 and -4.33 ± 1.46 at Day 169, while for dienogest, it was -2.47 ± 1.26 and -4.37 ± 1.28 , respectively. Likewise, the reductions in dysmenorrhoea and NMPP scores from baseline to Days 85 and 169 were comparable between both groups. At Day 169, the proportion of patients requiring rescue medication was comparable between the elagolix 150 mg and dienogest 2 mg groups ($p > 0.9999$) [22]. The EM-III and EM-IV extension trials evaluated the long-term efficacy and safety of elagolix for up to 12 months. At 6 months, the outcomes demonstrated that the long-term responder rates for dysmenorrhoea and NMPP were comparable to those observed in the EM-I and EM-II trials, indicating the sustained efficacy of elagolix in the management of EAP (Table 1) [21].

Expert opinion 1

Experts suggest that elagolix can be considered a probable first choice of treatment for patients with endometriosis who present with severe dysmenorrhoea or NMPP in clinical settings. Elagolix 150 mg can be prescribed for 6 months, after which the patient should be reassessed to determine the need for further therapy (up to 2 years). Reassessment should include treatment response and BMD. Although elagolix offers flexibility in dosing, further evidence is warranted.

Clinical response in dyspareunia

According to the EM-I and EM-II trials, at 3 months, the mean reduction in dyspareunia scores was significantly greater with elagolix 200 mg BID versus placebo [20]. The EM-III and EM-IV trials also demonstrated significant reductions in dyspareunia, with elagolix 150 mg OD and 200 mg BID at 6 and 12 months (Table 2) [21].

Table 2
Percentage of women with a clinically meaningful reduction in dyspareunia at 6 and 12 months.

	Percentage of women with a clinically meaningful reduction in dyspareunia at 6 and 12 months.	
	150 mg OD	200 mg BID
At 6 months		
EM-III	37.2%	58.7%
EM-IV	45.2%	60%
At 12 months		
EM-III	43.5%	62.0%
EM-IV	45.9%	58.1%

EM: Elaris Endometriosis; OD: Once daily; BID: Twice daily.

Expert opinion 2

Experts unanimously emphasised that treatment for endometriosis should address all symptoms, including dyspareunia and prevent recurrence. Elagolix has demonstrated significant efficacy in alleviating dyspareunia in patients with endometriosis.

Reduction in opioid usage

The EM-I and EM-II trials demonstrated that at 3 and 6 months, women receiving elagolix 200 mg BID used a significantly smaller amount of rescue analgesics than those on placebo, whereas with 150 mg OD, no significant reduction in analgesic use was observed [20]. Similarly, the EM-III and EM-IV trials showed that the average use of opioids decreased by 45.1% with elagolix 150 mg OD and 74.5% with a 200 mg BID over 12 months [21].

Clinical response to fatigue

A significant dose-dependent reduction in fatigue was observed with elagolix at 3 months, with a greater reduction noted at 6 months, based on the T-scores of the Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form 6a questionnaire (Table 3). The improvement was sustained over 12 months, as mean PROMIS T-scores in the extension study remained similar to those recorded at 6 months. There was a strong association between pain reduction and improvement in fatigue [23].

Impact on HRQoL

A post hoc analysis of the EM-I and EM-II trials evaluated HRQoL using the Endometriosis Health Profile-30 (EHP-30). After 6 months of treatment, notable improvements were noted across core scales: pain, control and powerlessness, emotional wellbeing, social support and self-image with elagolix 200 mg BID compared to placebo, with the highest improvements observed in pain and control and powerlessness. Elagolix 150 mg OD also enabled improvements across all subscales, except sexual intercourse, compared with placebo [24].

Women who responded to elagolix in the EM-I and EM-II trials for dysmenorrhoea showed a notable decrease in EHP-30 scores after 3 months, reflecting enhanced HRQoL. Patients who achieved a clinical response in dysmenorrhoea or NMPP also had fewer lost hours due to absenteeism at work and at home compared to those who did not achieve a clinical response (Table 4) [25].

Expert opinion 3

Experts unanimously agreed that elagolix results in pain relief, reduction in dyspareunia and resolution of deep infiltrating endometriosis (DIE), which can lead to a meaningful improvement in QoL.

Safety and tolerability of elagolix

Common adverse events

Elagolix has exhibited an acceptable safety profile. The most frequently reported adverse events (AEs) were hot flushes (mild-to-

Table 3

Change from baseline in PROMIS Fatigue Questionnaire T-scores at 3 and 6 months.

	150 mg OD	200 mg BID
At 3 months	-1.66 (95% CI -3.20 to -0.11; $p = 0.018$)	-4.23 (95% CI -5.82 to -2.65; $p < 0.001$)
At 6 months	-2.21 (95% CI -4.02 to -0.40; $p = 0.008$)	-5.90 (95% CI -7.74 to -4.06; $p < 0.001$)

OD: Once daily; BID: Twice daily; CI: Confidence interval.

Table 4

Weekly hours lost among responders and non-responders in EM-I and EM-II trials.

Results from both EM-I and EM-II trials	DYS responders*	DYS non-responders*	p -value
	0.6 (SE 0.4)	3.2 (SE 0.4)	EM-I: $p < 0.0001$; EM-II: $p = 0.0065$
	NMPP responders*	NMPP non-responders*	
	0.2 (SE 0.4)	3.2 (SE 0.4)	EM-I: $p < 0.0001$; EM-II: $p = 0.0605$

EM: Elaris Endometriosis; DYS: Dysmenorrhoea; NMPP: Non-menstrual chronic pelvic pain; SE: Standard Error.

* DYS or NMPP responders: A patient who met the pain reduction score threshold for dysmenorrhoea/NMPP at month 3 and did not have an increase in analgesic use.

* DYS or NMPP non-responders: A patient who did not meet the pain reduction score threshold for dysmenorrhoea/NMPP and/or had an increase in analgesic use at month 3.

moderate), headache and nausea. Treatment discontinuation due to hot flushes occurred in < 1% of women with elagolix 150 mg and in < 3% of women with elagolix 200 mg [20] Hot flush events continued in the EM-III and EM-IV trials. Elagolix can be safely used for a longer duration in patients with symptomatic endometriosis [21].

Impact on bone mineral density

In the EM-I and EM-II trials, both doses of elagolix showed notable mean decreases from baseline in BMD at the lumbar spine, femoral neck and total hip versus placebo at 6 months [20]. In the EM-III and EM-IV trials, >80% of women in the elagolix 150 mg group and > 40% of women in the elagolix 200 mg group had no change or an increase or a $\leq 3\%$ decrease from baseline in lumbar spine BMD at 12 months. The decrease in BMD was dose-dependent, with higher reductions reported with elagolix 200 mg BID. Further, no women in EM-III and only one woman treated with 200 mg in EM-IV had a Z-score below -2.0, highlighting long-term safety. Moreover, BMD returned toward baseline after treatment, with the fastest recovery with elagolix 200 mg BID. The reductions in BMD with elagolix were lower than those with leuprolide acetate, which showed a 6.3% mean decrease in lumbar spine BMD after 12 months [21].

Kilpatrick *et al.* reported that premenopausal elagolix treatment led to only a slight increase in long-term fracture risk and treatment threshold eligibility in postmenopausal women. The risk difference for osteoporotic or hip fractures between elagolix and comparator groups was similar (Table 5). With elagolix 150 mg OD for 12 months, the proportion of women reaching anti-osteoporotic treatment thresholds increased by age: 0.36% (ages 50–59), 0.23% (ages 60–69) and 1.79% (ages 70–79) [26].

Impact on menstrual bleeding patterns and ovulation

The effect of elagolix on menstrual bleeding demonstrated a dose-dependent reduction in the average number of bleeding and spotting days, as well as bleeding intensity in patients who reported menstrual

Table 5

Median risk of osteoporotic fractures due to elagolix treatment.

Age group (years)	Not treated with elagolix	Treated with elagolix 150 mg OD (1 year) or elagolix 200 mg BID (3 months)
50–59	4.70%	4.73%
60–69	6.79%	7.03%
70–79	10.68%	10.83%

OD: Once daily; BID: Twice daily.

bleeding (Table 6). A dose-dependent increase in the proportion of women experiencing amenorrhoea was also noted (Table 6). Over 3 menstrual cycles in healthy women, ovulation rates of approximately 50% and 32% were reported with elagolix 150 mg OD and 200 mg BID, respectively. After 12 months of treatment discontinuation, the rate of menstrual resumption was favourable with 150 mg OD and 200 mg BID [15].

Expert opinion 4

Experts opined that elagolix demonstrates a favourable safety profile while supporting regular menstruation and ovulation. Elagolix, particularly at the 150 mg dose, is associated with a higher likelihood of maintaining ovulation during therapy. Furthermore, menstrual cycles gradually resume after treatment cessation, with near-complete recovery by 6 months compared to Dienogest therapy.

Impact on pregnancy

Elagolix is not classified as a contraceptive despite its ability to suppress gonadotrophins and ovulation. Ovulation may still occur during elagolix treatment, especially at doses that only partially suppress ovarian oestrogen production [27]. Preclinical studies have shown that elagolix did not cause teratogenic effects [28].

Elagolix versus other therapies

Although currently available hormonal therapies have comparable effectiveness in relieving EAP, they vary in their safety profiles [29].

Oral contraceptive pills

Combined oestrogen–progestin oral contraceptive pills (OCs) have long been used as first-line treatment for endometriosis, despite limited evidence supporting their effectiveness [30]. Current OCP users have a lower risk of developing endometriosis, whereas past users show an increased risk [31]. Similarly, a higher incidence of endometriosis and a higher risk of DIE were observed among past OCP users. High oestrogen levels in OCPs may contribute to the progression of endometriosis to a more invasive form [32].

Dienogest

The FOGSI GCPR guidelines recommend dienogest as the first-line medical treatment for endometriosis [6]. However, despite its proven effectiveness, breakthrough bleeding remains a significant concern [33]. Harada *et al.* reported that all patients treated with dienogest experienced AEs. The most common AEs were breakthrough bleeding or spotting reported in 95% of patients, followed by hot flushes and headaches [34]. In a study by Nirgianakis *et al.*, 33% of participants reported breakthrough bleeding with dienogest, which was associated with treatment non-response and discontinuation. Primary dysmenorrhoea and suspected adenomyosis had a negative correlation with treatment response [35]. McCormack *et al.* reported that dienogest 2 mg resulted in endometrial regression and menstrual bleeding irregularities [36]. In another study, around 20% of patients experienced irregular

Table 6
Effect of elagolix on menstrual bleeding patterns.

	Elagolix 150 mg OD	Elagolix 200 mg BID
After 6 months of treatment		
Maintenance of the menstrual cycle	~ 83%	~ 48%
Amenorrhoea	6%–17%	13%–52%
After 12 months of therapy, the resumption of menses after stopping treatment		
1 st month of treatment	77%	55%
2 nd month of treatment	95%	91%
6 th month of treatment	98%	96%

OD: Once daily; BID: Twice daily.

bleeding patterns within the first 3 months of treatment [37]. Additionally, worldwide progestin therapy fails to achieve symptom control in nearly one-third of women, due to progesterone resistance [9].

A randomised controlled phase 3 trial of elagolix and dienogest reported that elagolix 150 mg was non-inferior to dienogest 2 mg in reducing the NRS score for dysmenorrhoea and NMPP. The incidence of treatment-emergent adverse events (TEAEs) was also similar in both groups, with no serious AEs reported [22].

Expert opinion 5

According to the experts, the primary side effect associated with dienogest is breakthrough bleeding. Additionally, it can lead to mood changes, particularly irritability and may induce amenorrhoea lasting up to 6 months. A subset of patients shows no response to progestin therapy due to progestin resistance. In such scenarios, experts recommend considering elagolix 150 mg as a potential first-line treatment option for managing EAP.

Injectable leuprolide

In EAP, GnRH agonists such as leuprolide are considered second-line treatments. However, BMD loss and osteoporosis are the most common AEs, along with severe hypo-oestrogenic symptoms often requiring add-back therapy [38]. In comparison with Leuprolide, hot flushes were less frequent with elagolix. The rates of hot flushes with leuprolide acetate have been reported to be as high as 84% [39]. Adverse events were more frequent with leuprolide acetate, both alone and with add-back therapy, compared to elagolix [40].

Poulos *et al.* evaluated the preferences of patients with EAP and reported that, compared to Leuprolide, the probability of choosing elagolix 150 mg daily was 51.6% in respondents with moderate-to-severe hot flashes and 60.7% in those without moderate-to-severe hot flushes. Similarly, the probability of choosing elagolix 200 mg over leuprolide was 82.6% with hot flushes and 92.6% without hot flushes [41]. After 12 months of treatment in Elaris EM-III, the mean percentage reduction from baseline in lumbar spine BMD was -0.63% in the 150 mg OD group (-1.10% in Elaris EM-IV) and -3.60% in the 200 mg BID group (compared with -3.91% in Elaris EM-IV). No participants in Elaris EM-III and only one participant receiving elagolix 200 mg BID in Elaris EM-IV had a Z-score below -2.0 . Among individuals who underwent dual-energy X-ray absorptiometry (DXA) assessment during the post-treatment phase of Elaris EM-IV, lumbar spine BMD Z-scores (median and quartiles) demonstrated a trend toward improvement in the 200 mg BID group [21]. In contrast, BMD loss with leuprolide monotherapy persisted longer, which was lessened by add-back therapy [39].

After 6 months of treatment with elagolix 150 mg OD, menses resumed in 59%, 87% and 95% of women within 1, 2 and 6 months following discontinuation, respectively. Similarly, with elagolix 200 mg BID, resumption rates were 60%, 88% and 97% at the same time points [15]. In comparison, leuprolide 3.75 mg monthly showed resumption of normal menstrual cycles in 7%, 71% and 95% of patients during the 1, 2 and 3 months after treatment cessation, respectively, excluding those who became pregnant. Leuprolide 3.75 mg induced amenorrhoea in 74% of patients after the 1st month and in 98% after the 2nd month of treatment. However, the incidence of amenorrhoea with Elagolix during the first six months of therapy ranged from 6 to 17% with 150 mg once daily and 13–52% with 200 mg twice daily [15,39].

Expert opinion 6

Experts recommend that body weight, oestrogen levels and BMD should be assessed before initiating elagolix and repeated after 6 months of treatment. Supplementation with calcium and vitamin D, along with lifestyle modifications to support bone health, should be encouraged for all women receiving elagolix.

Injectable medroxyprogesterone

Carr *et al.* compared the effects of elagolix and subcutaneous depot

medroxyprogesterone acetate (DMPA-SC) on BMD in women with EAP. At week 24, the mean percentage change in BMD for the spine was -0.11% with 150 mg OD and -1.29% with 75 mg BID, compared to baseline. For the femur, the corresponding changes were -0.47% and -1.02% , respectively. In comparison with DMPA-SC, the changes were -0.99% for the spine and -1.29% for the femur at week 24. Thus, there were minimal effects on BMD with elagolix and DMPA-SC. Elagolix was non-inferior to DMPA-SC in improving EAP and was associated with less uterine bleeding [28].

A network meta-analysis of 31 randomised controlled trials (RCTs) concluded that elagolix alone was one of the most effective treatments for reducing dysmenorrhoea and dyspareunia compared to other options, such as injectable GnRH agonists, other oral GnRH antagonists, progestins, combined oral contraceptive (COC) pills and placebo (SMD: -2.89 , 95% CI: -5.28 to -0.50). In terms of dyspareunia, elagolix was the only treatment that showed a significant improvement versus placebo (SMD: -1.32 , 95% CI: -2.55 to -0.08). Elagolix monotherapy was found to be more effective than elagolix combined with add-back therapy [42].

Expert opinion 7

Experts agreed that, in comparison to current therapies, elagolix shows a more favourable safety profile and is non-inferior in terms of efficacy, while offering the added benefit of convenient oral administration for the management of EAP. In cases of scar endometriosis, elagolix has shown potential to enable pain resolution.

Elagolix with add-back therapy

To minimise the impact of hypoestrogenic effect on BMD, the use of “add-back” hormonal replacement therapy (ABT) has been recommended alongside GnRH antagonist treatment [13]. ABT, consisting of 1 mg oestradiol and 0.5 mg norethindrone acetate OD, has been shown to mitigate hypoestrogenic effects associated with elagolix. An ongoing Phase 3 trial assessed the efficacy, tolerability and BMD outcomes of elagolix with ABT in the treatment of EAP. For dysmenorrhoea, responder rates using last observation carried forward (LOCF) to impute missing data were 62.8% in the elagolix plus ABT group compared with 23.7% in the placebo group ($p < 0.001$). For NMPP, LOCF-based responder rates were 51.3% with elagolix plus ABT versus 36.8% with placebo ($p < 0.001$). At months 6 and 12, the mean percentage change in BMD from baseline with elagolix plus ABT remained $< 1\%$ and was comparable to placebo across all anatomical sites [18].

Adenomyosis and heavy menstrual bleeding

Approximately 20% of adenomyosis cases occur in women under 40 years of age [43]. Elagolix has emerged as a promising treatment for adenomyosis, effectively reducing heavy menstrual bleeding (HMB). Jubaida *et al.* reported that after 3 months, the mean Visual Analogue Scale (VAS) score decreased significantly more with elagolix 200 mg OD than with dienogest 2 mg OD in patients with symptomatic adenomyosis. HMB was reported in only 3.7% of patients taking elagolix versus 23.1% taking dienogest ($p < 0.05$) [44]. The first case report of elagolix 150 mg/day in uterine adenomyoma described a 41-year-old woman who experienced complete resolution of pelvic pain and no discernible mass associated with diffuse adenomyosis a month post-treatment, highlighting its debulking effect [45].

Expert opinion 8

In clinical practice, notable reductions in uterine size have been observed in patients with adenomyosis; however, more robust clinical evidence is needed to substantiate these findings.

Pre- or post-laparoscopic surgery in endometriosis

Laparoscopic excision poses a major challenge of disease recurrence post-surgery. A meta-analysis confirmed that 6 months of post-surgical

GnRH analogue therapy reduced the risk of endometriosis recurrence [46]. The 2024 FOGSI-ICOG GCPR guidelines recommend elagolix for the management of DIE-associated symptoms, with notable improvements when administered either before or after surgery [6].

Expert opinion 9

According to experts, elagolix offers the advantage of faster reversal of hormonal levels following treatment discontinuation compared to GnRH agonists. This is particularly beneficial for women undergoing laparoscopic surgery for endometriosis, as it facilitates quicker return of reproductive function and enhances the chances of conception. Elagolix could be considered a valuable therapy for both pre- and post-laparoscopic management in endometriosis.

Conclusion

Elagolix has emerged as a promising therapeutic approach, offering a significant reduction in EAP and improvement in QoL for women affected by endometriosis. Compared to conventional interventions, elagolix demonstrates a superior safety profile with fewer incidences of hypo-oestrogenic effects. Backed by robust clinical evidence and endorsed by FOGSI, elagolix could be considered a potential future first-line treatment option for EAP, marking an important step forward in modern gynaecological care.

Sources of Funding

None.

CRediT authorship contribution statement

Sunita Tandulwadkar: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Formal analysis, Data curation, Conceptualization. **Basab Mukherjee:** Writing – review & editing, Visualization, Validation, Formal analysis, Data curation, Conceptualization. **Chaitanya Ganpule:** Writing – review & editing, Visualization, Validation, Formal analysis, Data curation, Conceptualization. **Madhuri Patel:** Writing – review & editing, Visualization, Validation, Formal analysis, Data curation, Conceptualization. **Subash Mallya:** Writing – review & editing, Visualization, Validation, Formal analysis, Data curation, Conceptualization. **P.M. Gopinath:** Writing – review & editing, Visualization, Validation, Formal analysis, Data curation, Conceptualization. **Brajbala Tiwari:** Writing – review & editing, Visualization, Validation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors Sunita Tandulwadkar, Basab Mukherjee and Chaitanya Ganpule, Madhuri Patel, Subash Mallya, P. M. Gopinath, and Brajbala Tiwari provided key clinical insights, collected data and critically revised the manuscript. Additionally, the experts Abhinimesh Chatterjee, Ashwini Kale, Dibyendu Banerjee, Jayam Kanan, J. B. Sharma, Kailash Ochwani, K. U. Kunjimoideen, Mehul Sukhadiya, Nilesh Balkawade, Prashanth Adiga, Rajendra Nagarkatti, R. M. Saraogi and Sampath Kumari contributed to providing clinical insights and critically reviewing the manuscript. Writing and editorial support were provided by Scientimed Solutions Pvt. Ltd.

References

- [1] Gajbhiye RK. Endometriosis and inflammatory immune responses: Indian experience. *Am J Reprod Immunol* 2023;89(2):e13590.
- [2] Bourdel N, Chauvet P, Billone V, Douridas G, Fauconnier A, Gerbaud L, et al. Systematic review of quality of life measures in patients with endometriosis. *PLoS One* 2019;14(1):e0208464.
- [3] Chantalat E, Valera MC, Vaysse C, Noirrit E, Rusidze M, Weyl A, et al. Estrogen receptors and endometriosis. *Int J Mol Sci* 2020;21(8):2815.
- [4] Pontoppidan K, Olovsson M, Grundström H. Clinical factors associated with quality of life among women with endometriosis: a cross-sectional study. *BMC Womens Health* 2023;23(1):551.
- [5] Rafique S, Decherney AH. Medical management of endometriosis. *Clin Obstet Gynecol* 2017;60(3):485–96.
- [6] FOGSI-ICOG Good Clinical Practice Recommendations (G CPR) Updates in Endometriosis Management. [Cited 2025 September 16]. Available from: <https://www.fogsi.org/wp-content/uploads/2024/11/G CPR-Updates-in-Endometriosis-Management.pdf>.
- [7] Becker CM, Bokor A, Heikinhoimo O, Horne A, Jansen F, Kiesel L, et al. ESHRE guideline: Endometriosis. *Hum Reprod Open*. 2022;2022(2):hoac009.
- [8] García-Sáenz M, Ibarra-Salce R, Pozos-Varela FJ, Mena-Ureta TS, Flores-Villagómez S, Santana-Mata M, et al. Understanding progestins: from basics to clinical applicability. *J Clin Med* 2023;12(10):3388.
- [9] Zhang P, Wang G. Progesterone resistance in endometriosis: current evidence and putative mechanisms. *Int J Mol Sci* 2023;24(8):6992.
- [10] Divasta AD, Laufer MR, Gordon CM. Bone density in adolescents treated with a GnRH agonist and add-back therapy for endometriosis. *J Pediatr Adolesc Gynecol* 2007;20(5):293–7.
- [11] Leyland N, Estes SJ, Lessey BA, Advincula AP, Taylor HS. A clinician's guide to the treatment of endometriosis with elagolix. *J Womens Health (Larchmt)* 2021;30(4):569–78.
- [12] Barbieri RL. Hormone treatment of endometriosis: the estrogen threshold hypothesis. *Am J Obstet Gynecol* 1992;166(2):740–5.
- [13] Viviano M, Benagiano G, Guo SW, Pluchino N. Why do oestrogens matter: Systematic review and meta-analysis assessing GnRH antagonists, considering add-back therapy, for endometriosis-associated pain. *Reprod Biomed Online* 2024;49(4):104321.
- [14] Rzewuska AM, Żybowska M, Sajkiewicz I, Spiechowicz I, Żak K, Abramiuk M, et al. Gonadotropin-releasing hormone antagonists—a new hope in endometriosis treatment? *J Clin Med* 2023;12(3):1008.
- [15] Orilissa PI. Highlights of prescribing information. [Cited 2025 September 16]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210450s0001bl.pdf.
- [16] AbbVie. AbbVie receives Health Canada approval of ORILISSA™ (elagolix) for the treatment of moderate to severe pain associated with endometriosis. [Cited 2025 September 16]. Available from: https://www.abbvie.ca/content/dam/abbvie-dotcom/ca/en/documents/press-releases/2018-Oct-5_Elagolix-Health-Canada-Release_EN.pdf.
- [17] Recommendations of the SEC (Reproductive) made in its 02nd/24 meeting held on 20.03.2024 at CDSCO (HQ), New Delhi. [Cited 2025 September 16]. Available from: <https://cdsco.gov.in/opencms/resources/UploadCDSCOWeb/2018/UploadCommitteeFiles/Recommendations%20Reproductive%20dated%2020.03.2024.pdf>.
- [18] Miller CE, Kim JH, Kroll R, Simon JA, Soliman AM, Thomas JW, et al. Efficacy, tolerability, and bone density outcomes of elagolix with add-back therapy for endometriosis-associated pain: twelve months of an ongoing randomized phase 3 trial. *Am J Obstet Gynecol* 2024;231(6):630.e1–630.e13.
- [19] Ng J, Chwalisz K, Carter DC, Klein CE. Dose-dependent suppression of gonadotropins and ovarian hormones by elagolix in healthy premenopausal women. *J Clin Endocrinol Metab* 2017;102(5):1683–91.
- [20] Taylor HS, Giudice LC, Lessey BA, Abrao MS, Kotarski J, Archer DF, et al. Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist. *N Engl J Med* 2017;377(1):28–40.
- [21] Surrey E, Taylor HS, Giudice L, Lessey BA, Abrao MS, Archer DF, et al. Long-term outcomes of elagolix in women with endometriosis: results from two extension studies. *Obstet Gynecol* 2018;132(1):147–60.
- [22] Gupta N, Palve T, Kamilya G, Srivastava S, Malathi P, Bohir S, et al. Efficacy and safety of elagolix in endometriosis: Phase-III randomized double-blind active-controlled trial BJOG-An. *Int J Obs and Gynaec* 2024;131:3.
- [23] Surrey ES, Soliman AM, Agarwal SK, Snabes MC, Diamond MP. Impact of elagolix treatment on fatigue experienced by women with moderate to severe pain associated with endometriosis. *Fertil Steril* 2019;112(2):298–304.e3.
- [24] Taylor HS, Soliman AM, Johns B, Pokrzywinski RM, Snabes M, Coyne KS. Health-related quality of life improvements in patients with endometriosis treated with elagolix. *Obstet Gynecol* 2020;136(3):501–9.
- [25] Pokrzywinski RM, Soliman AM, Chen J, Snabes MC, Coyne KS, Surrey ES, et al. Achieving clinically meaningful response in endometriosis pain symptoms is associated with improvements in health-related quality of life and work productivity: analysis of 2 phase III clinical trials. *Am J Obstet Gynecol* 2020;222(6):592.e1–592.e10.
- [26] Kilpatrick RD, Chiuv SE, Leslie WD, Wegrzyn LR, Gao W, Yang H, et al. Estimating the effect of elagolix treatment for endometriosis on postmenopausal bone outcomes: a model bridging phase III trials to an older real-world population. *JBM Plus* 2020;4(12):e10401.
- [27] Shebley M, Polepally AR, Nader A, Ng JW, Winzenborg I, Klein CE, et al. Clinical pharmacology of elagolix: an oral gonadotropin-releasing hormone receptor antagonist for endometriosis. *Clin Pharmacokinet* 2020;59(3):297–309.
- [28] Carr B, Dmowski WP, O'Brien C, Jiang P, Burke J, Jimenez R, et al. Elagolix, an oral GnRH antagonist, versus subcutaneous depot medroxyprogesterone acetate for the treatment of endometriosis: effects on bone mineral density. *Reprod Sci* 2014;21(11):1341–51.
- [29] Vercellini P, Viganò P, Barbara G, Buggio L, Somigliana E. 'Luigi mangiagalli' endometriosis study group. elagolix for endometriosis: all that glitters is not gold. *Hum Reprod* 2019;34(2):193–9.
- [30] Casper RF. Progestin-only pills may be a better first-line treatment for endometriosis than combined estrogen-progestin contraceptive pills. *Fertil Steril* 2017;107(3):533–6.
- [31] Vercellini P, Eskenazi B, Consonni D, Somigliana E, Parazzini F, Abbiati A, et al. Oral contraceptives and risk of endometriosis: a systematic review and meta-analysis. *Hum Reprod Update* 2011;17(2):159–70.
- [32] Chapron C, Souza C, Borghese B, Lafay-Pillet MC, Santulli P, Bijaoui G, et al. Oral contraceptives and endometriosis: the past use of oral contraceptives for treating severe primary dysmenorrhea is associated with endometriosis, especially deep infiltrating endometriosis. *Hum Reprod* 2011;26(8):2028–35.
- [33] Liu JY, Sheu BC, Chang CY, Yen CF, Wu MH, Chen YJ, et al. Long-term dienogest treatment in endometriosis: consensus from Taiwanese experts. *Taiwan J Obstet Gynecol* 2024;63(6):823–5.
- [34] Harada T, Momoeda M, Taketani Y, Aso T, Fukunaga M, Hagino H, et al. Dienogest is as effective as intranasal buserelin acetate for the relief of pain symptoms associated with endometriosis—A randomized, double-blind, multicenter, controlled trial. *Fertil Steril* 2009;91(3):675–81.
- [35] Nirgianakis K, Vaineau C, Agliati L, McKinnon B, Gasparri ML, Mueller MD. Risk factors for non-response and discontinuation of dienogest in endometriosis patients: a cohort study. *Acta Obstet Gynecol Scand* 2021;100(1):30–40.
- [36] McCormack PL. Dienogest: a review of its use in the treatment of endometriosis. *Drugs* 2010;70(16):2073–88.
- [37] Strowitzki T, Faustmann T, Gerlinger C, Schumacher U, Ahlers C, Seitz C. Safety and tolerability of dienogest in endometriosis: pooled analysis from the European clinical study program. *Int J Womens Health* 2015;7:393–401.
- [38] Patel M. Recent trends in medical management of endometriosis. *J Obstet Gynaecol India* 2024;74(6):479–83.
- [39] LUPRON DEPOT PI. [Cited 2025 September 16]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/019732s045,020517s0431bl.pdf.
- [40] Wang ST, Johnson SJ, Mitchell D, Soliman AM, Vora JB, Agarwal SK. Cost-effectiveness of elagolix versus leuprolide acetate for treating moderate-to-severe endometriosis pain in the USA. *J Comp Eff Res* 2019;8(5):337–55.
- [41] Poulos C, Soliman AM, Renz CL, Posner J, Agarwal SK. Patient preferences for endometriosis pain treatments in the United States. *Value Health* 2019;22(6):728–38.
- [42] Kou L, Huang C, Xiao D, Liao S, Li Y, Wang Q. Pharmacologic interventions for endometriosis-related pain: a systematic review and meta-analysis. *Obstet Gynecol* 2025;146(2):e23–35.
- [43] Harada T, Khine YM, Kaponis A, Nikellis T, Decavalas G, Taniguchi F. The impact of adenomyosis on women's fertility. *Obstet Gynecol Surv* 2016;71(9):557–68.
- [44] Muhammad J, Yusof Y, Ahmad I, Norhayati MN. Elagolix treatment in women with heavy menstrual bleeding associated with uterine fibroid: a systematic review and meta-analysis. *BMC Womens Health* 2022;22(1):14.
- [45] Kavoussi SK, Esqueda AS, Jukes LM. Elagolix to medically treat a uterine adenomyoma: a case report. *Europ J Obs Gyn Rep Bio* 2020;247:266–7.
- [46] Koga K, Osuga Y, Takemura Y, Takamura M, Taketani Y. Recurrence of endometrioma after laparoscopic excision and its prevention by medical management. *Front Biosci (Elite Ed)* 2013;5(2):676–83.