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Clinical Guidance Paper VVOG: Pharmacological treatment of endometriosis-related pain

Objective of the clinical guidance paper

The present clinical guidance paper focuses on the pharmacological treatment of endometriosis-related pain in women in Flanders.

Summary of Recommendations

Treatment	Recommendation	G Level of Evidence
A. Analgesics		
NSAIDs or other analgesics (alone or in combination with other treatments) for endometriosis-related pain	xxx	+
B. Hormonal treatment		
Hormonal treatment (combined hormonal contraception, progestogens, GnRH agonists or GnRH antagonists) for endometriosis-related pain	xxxx	+ ++
Choice of hormonal treatment based on individual preferences, side effects, individual effectiveness, cost and availability	GCP	+
B1. Combined hormonal contraception		
Combined hormonal contraception (oral, vaginal or transdermal) for endometriosis-related pain	xxxx	+ +
Continuous use of combined hormonal contraception for endometriosis-related dysmenorrhea	xxx	+ +
B2. Progestogens		
Oral progestogens for endometriosis-related pain	xxxx	+ +
Levonorgestrel-releasing intrauterine system or etonogestrel-releasing subdermal implant for endometriosis-related pain	xxxx	+ ++
B3. GnRH agonists		
GnRH agonists for endometriosis-related pain, though evidence is limited regarding dosage or treatment duration	xxxx	+ +
GnRH agonists only as second-line treatment based on good clinical practice (e.g. when hormonal contraception or progestogens are ineffective), due to their side effect profile, especially without add-back therapy	GCP	+
Prescribe combined hormonal add-back therapy with GnRH agonists to prevent bone loss and hypo-estrogenic symptoms	xxxx	+ ++
B4. GnRH antagonists		
GnRH antagonists for endometriosis-related pain, with growing evidence regarding dosage	xxxx	+ ++
GnRH antagonists only as second-line treatment based on good clinical practice (e.g. when hormonal contraceptives or progestogens are ineffective), due to their side effect profile, especially without add-back therapy	GCP	+
Prescribe combined hormonal add-back therapy with GnRH antagonists to prevent bone loss and hypo-estrogenic symptoms	xxxx	+ ++
B5. Aromatase inhibitors		
Aromatase inhibitors for women with endometriosis-related pain who do not respond to other medical or surgical treatments (off-label). In premenopausal women, only in combination with an ovulation-suppressing agent.	xxxx	+ +
C. Prevention of recurrent endometriosis		
Levonorgestrel-releasing intrauterine system or combined hormonal contraception as secondary prevention of endometriosis-related dysmenorrhea postoperatively in women without childbearing wishes, for at least 18–24 months	xxxx	+ +
Long-term hormonal treatment as secondary prevention of endometriomas and postoperative symptom recurrence in women without childbearing wishes	xxxx	+ +
Long-term hormonal treatment as secondary prevention of deep endometriosis and associated symptoms postoperatively in women without childbearing wishes	xxx	+

Symbols Used for Recommendations and Level of Evidence

Strength of Recommendation	Level of Evidence
xxxx: strong recommendation for	+ ++ +: high
xxx: weak recommendation for	+ ++ : moderate
xx: weak recommendation against	+ +: low
x: strong recommendation against	+: very low
GCP: Good Clinical Practice	–: indirect or no evidence

Acronyms and Abbreviations

ADAPTE tool, A tool for guideline development by adapting existing high-quality guidelines; AGREE tool, Appraisal of Guidelines for Research and Evaluation; BMD, Bone Mineral Density; DE, Deep Endometriosis; EHP, Endometriosis Health Profile questionnaire; ESHRE, European Society of Human Reproduction and Embryology; GCP, Good Clinical Practice; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NSAID, Non-Steroidal Anti-Inflammatory Drug; NMPP, Non-Menstrual Pelvic Pain; VAS, Visual Analogue Scale; VVOG, Flemish Society of Obstetrics and Gynaecology; VWAG, Flemish Working Group on General Gynaecology of the VVOG

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Background

Endometriosis is a condition in which tissue resembling endometrium (stromal or epithelial tissue) is located outside the endometrium and myometrium, typically associated with an inflammatory process. There are three distinct types of endometriotic lesions: ovarian (endometrioma), peritoneal, and deep infiltrating endometriosis (DE). These lesions are mainly found in the pelvic cavity near by the ovaries, vagina, bladder, rectum, rectovaginal septum, rectosigmoid, pouch of Douglas and uterosacral ligaments, although the disease can also occur in extrapelvic locations [1–4].

It is an estrogen-dependent condition, thus more commonly affecting women of reproductive age. The exact prevalence is unknown but is estimated to range from 2 % to 10 % in the general population, increasing to 50 % in infertile women and women with chronic lower abdominal pain [1,2].

The condition may be asymptomatic; however, two-thirds of women with endometriosis experience pelvic pain symptoms (chronic pelvic pain, dysmenorrhea, lower back pain, dyspareunia, or dyschezia). Another common symptom is infertility. Among women with known dysmenorrhea, 5–15 % report pain so severe that it interferes with daily life, leading to absence from work or school [5,6].

> Rationale

Endometriosis-related pain significantly affects various aspects of quality of life (including sexual, social, and work-related domains) as well as the mental health of patients. Timely treatment of endometriosis-related pain can improve overall quality of life.

> Objective

The objective of this clinical guidance is to provide an Evidence-Based Medicine tool for Flemish gynaecologists and residents in training regarding the pharmacological treatment of endometriosis-related pain in women.

> Target Audience

The target audience of this clinical guidance includes Flemish general gynaecologists and gynaecology residents

Development of the Clinical Guidance

Since the publication of the previous clinical guidance paper on the diagnosis of endometriosis, no new international guidelines have been developed. For the previous guidance, a literature review was performed, during which known guidelines were evaluated using the AGREE II method. Based on this, it was decided to use the ESHRE guideline from 2022 due to its reliability, clarity, and recency, with literature included up to 2020.

The current clinical guidance paper is also based on the revised ESHRE guideline (2022). It was adapted to Flemish clinical practice using the ADAPTE methodology. An additional literature review covering the period from January 2021 to September 2024 was conducted using PUBMED and Cochrane. Only systematic reviews, meta-analyses, randomized controlled trials (RCTs) and clinical trials available in English were included.

Evidence and Recommendations

A. The use of analgesics for the relief of endometriosis-related pain (recommendation: xxx; evidence: +)

Analgesics such as paracetamol or NSAIDs are considered first-line treatments for endometriosis-related pain due to their favorable safety profile and accessibility. However, their effectiveness is demonstrated in only one study, which is of low quality and limited evidence. They may be used alone or in combination with hormonal or surgical therapy [7,8].

There is no evidence supporting the use of neuromodulators (e.g., tricyclic antidepressants, selective serotonin reuptake inhibitors or anticonvulsants) in the treatment of endometriosis-related pain [9,10].

Recommendation:

Weak for: The panel suggests that NSAIDs or other pain relievers may be offered (alone or in combination with other treatments) to reduce endometriosis-related pain.

B. The use of hormonal treatments in the management of endometriosis-related pain (recommendation: xxxx; evidence: +++)

As endometriosis is an estrogen-dependent condition, hormonal therapy is often initiated as pain treatment —sometimes empirically, even without imaging or surgical confirmation—or postoperatively to prevent recurrence. These treatments create a hypo-estrogenic environment through ovarian suppression or act directly on steroid receptors or enzymes within the lesions to inhibit disease progression. All available treatments are suppressive rather than curative; symptoms typically return upon cessation [1].

Studies included in the National Institute for Health and Care Excellence (NICE) guideline (2017) report significant pain reduction when using these hormonal treatments versus placebo, based on Visual Analog Scale (VAS) pain scores for non-menstrual pelvic pain (NMPP) and dysmenorrhea. Reduction is similar across all hormonal options.

Because each treatment has different side effects that are often individually determined, finding the most suitable therapy for each patient is a matter of trial and error. Contraceptive effects should also be considered in the decision-making process [11]. (recommendation: GCP; evidence: +)

Recommendation:

Strong: The panel recommends offering women a hormonal treatment (combined hormonal contraception, progestogens, GnRH agonists, or GnRH antagonists) as one of the options to relieve endometriosis-related pain.

GCP: The panel recommends considering individual preferences, side effects, personal effectiveness, cost, and availability when selecting hormonal treatments.

B1. Combined Hormonal Contraceptives

Effectiveness (recommendation: xxxx; evidence: ++)

Systematic reviews demonstrate a significant reduction in dysmenorrhea, dyspareunia and NMPP, as well as improved quality of life with oral combined contraceptives [12–14].

Continuous use (recommendation: xxx; evidence: ++)

Continuous use of oral combined contraceptives leads to amenorrhea and a more stable hormonal environment, providing more effective relief from dysmenorrhea (RR 0.24; 95 % CI 0.06–0.91) and reducing endometrioma recurrence (RR 0.54; 95 % CI 0.28–1.05). However, there are no significant differences between cyclic and continuous use in terms of dyspareunia and NMPP [6,15,16].

Safety

Continuous intake does not appear to have additional adverse effects on coagulation or (bone) metabolism, including bone mineral density (BMD), compared to cyclic use. Arterial complications were not studied [17].

Route of administration

There is limited evidence regarding preferences for the route of hormonal therapy, making it difficult to provide concrete recommendations. Two studies have explored this, Vercellini et al. (2010) found that after 48 weeks, a transdermal patch (ethinylestradiol 20 mg + norelgestromin 150 mg/day) was more effective than a vaginal ring (ethinylestradiol 15 mg + etonogestrel 120 mg/day). Leone et al. (2014) on the other hand showed that, for women with deep endometriosis, desogestrel-only pills were preferred over sequential contraceptive vaginal rings after 48 weeks due to better management of endometriosis-related gastrointestinal symptoms [18,19].

Conclusion

Combined oral contraceptives are recommended for the treatment of endometriosis-related pain due to their effectiveness, safety and cost. A major additional benefit is their contraceptive effect.

Recommendations:

Strong for: The panel recommends prescribing combined hormonal contraception (oral, vaginal, or transdermal) to relieve endometriosis-related pain.

Weak for: Continuous use of combined hormonal contraception may be considered for women suffering from endometriosis-related dysmenorrhea.

B2. Progestogens

Effectiveness (recommendation: xxxx; evidence: ++)

A Cochrane review by Brown et al. (2012) found limited evidence that continuous use of progestogens is effective for treating endometriosis-related pain, without a clear preference for any specific oral progestogen. Continuous use induces decidualization and subsequent atrophy of endometriotic lesions [20,21].

Most recent studies have focused on dienogest. These studies show that dienogest 2 mg/day and combined oral contraceptives (e.g., 0.03 mg ethinylestradiol + 3 mg drospirenone; 0.03 mg ethinylestradiol + 0.15 mg levonorgestrel; 1.5 mg 17β-estradiol + 2.5 mg nomegestrol acetate) provide similar significant improvements in pain and quality of life compared to placebo. Only one study by Piacenti et al. (2021) reported greater pain reduction with dienogest than with a combined oral contraceptive (0.02 mg ethinylestradiol + 0.1 mg levonorgestrel). Another study showed higher quality of life and female sexual function index (FSFI) scores with dienogest after 6 and 12 months [22–25].

Safety:

Patients using oral progestogens report more amenorrhea and intermenstrual bleeding [20]. A pooled analysis of 4 studies confirmed that dienogest 2 mg is safe for up to 65 weeks, with mild to moderate side effects like headache, breast tenderness, depressive symptoms, and acne in fewer than 10 % of cases. Prolonged use up to 5 years was also found to be safe [26,27].

Depot progestogens are associated with more bloating, nausea, weight gain, intermenstrual bleeding, and amenorrhea, in addition to injection-site reactions. LNG-IUDs are linked to higher rates of irregular vaginal bleeding (26.8 %) compared to oral formulations [20,28].

Long-Term Use:

Long-term use of dienogest 2 mg/day significantly reduces endometriosis-related pain. The longer the duration of use, the more effective the reduction. During the first six months, a small decrease in BMD is observed; however, this is minimal and does not contraindicate long-term use in healthy reproductive-aged women [29,30].

Route of Administration:

Studies comparing the intrauterine system and subdermal implant showed neither is superior in terms of pain relief. It's worth noting that the LNG-IUD works without suppressing ovulation, whereas systemic options do [28,31–33].

Recommendations:

Strong for: The panel recommends prescribing progestogens to reduce endometriosis-related pain

Strong for: The panel recommends prescribing a levonorgestrel-releasing intrauterine system or an etonogestrel-releasing subdermal implant to reduce endometriosis-related pain.

B3. GnRH Agonists

Effectiveness (recommendation: xxxx; evidence: ++)

A recent Cochrane review by Veth et al. (2023), published after the release of the ESHRE guidelines, concluded that GnRH agonists are more effective than placebo or oral/injectable progestins in reducing dysmenorrhea, NMPP, dyspareunia, and pelvic tenderness after three months of treatment. No studies are available comparing GnRH agonists with no treatment, analgesics, or an LNG-IUD [34].

Only one trial by Vercellini et al. (1993) compared oral combined contraceptives with a GnRH agonist (goserelin), showing no significant difference in pain reduction. However, this study has low-quality evidence due to its small population size [16].

Safety

GnRH agonists are associated with several side effects that can significantly impact quality of life. Common adverse effects include vaginal dryness, hot flashes, weight gain, headaches, acne and bone loss. Bone loss is dose- and duration-dependent. For instance, an RCT by Tang et al. (2017) showed that treatment with a full dose of leuprorelin (3.75 mg) resulted in significantly greater BMD loss after 20 weeks compared to a half-dose (5.6 % vs 2.1 %) [35,36].

Add-back therapy (recommendation: xxxx; evidence: ++)

Add-back therapy is used to prevent bone loss and hypoestrogenic side effects of GnRH agonists while maintaining therapeutic efficacy. This may involve progestin monotherapy, combined estrogen-progestin therapy, selective estrogen receptor modulators, bisphosphonates, tibolone, or testosterone [37]. A meta-analysis by Wu et al. (2014) demonstrated that lumbar spine BMD—being the most estrogen-sensitive region—is higher in women treated with add-back therapy alongside GnRH agonists than without. No difference was observed for femoral neck BMD between the groups [38].

Reimbursement criteria

In Belgium, goserelin (subcutaneous implant) and triptorelin (injectable extended-release suspension) are reimbursed without prior authorization and without time limits (category A) for the symptomatic treatment of endometriosis [39].

Recommendation

GCP: The panel recommends prescribing GnRH agonists only as second-line therapy (e.g., when hormonal contraception or progestins are ineffective) due to their cost, lack of first-line evidence, and side effects (especially without add-back).

Strong for: The panel recommends prescribing GnRH agonists to women to reduce endometriosis-related pain, although evidence on dosing and duration is limited.

Strong for: The panel recommends prescribing combined hormonal add-back therapy alongside GnRH agonists to prevent bone loss and hypoestrogenic symptoms.

B4. GnRH antagonists (recommendation: xxxx; evidence: ++)

GnRH antagonists—such as elagolix, linzagolix, and relugolix—are promising new options for the treatment of endometriosis-related pain. Their pain-reducing efficacy is dose-dependent and comparable to that of GnRH agonists for dysmenorrhea and NMPP. Advantages include oral administration, rapid onset without a flare-up effect, and reversibility. However, similar side effects are observed, particularly BMD loss, which limits the duration of treatment (max. 6–12 months) if used without add-back therapy. Adding back therapy allows for longer treatment duration due to reduced BMD loss [38,40–42].

The SPIRIT 1 and 2 long-term studies (up to 2 years) show a positive effect of relugolix 40 mg with add-back therapy (1 mg estradiol / 0.5 mg norethisterone acetate) on endometriosis-related pain, with a favorable safety profile for bone health during prolonged use. These studies regard a < 1 % BMD loss from baseline as clinically insignificant. While a small initial BMD decline (<1 %) is observed, it remains stable thereafter. Menstrual cycles typically resume within two months after discontinuation—faster than with long-term use of GnRH agonists. Studies investigating add-back therapy with linzagolix and elagolix are ongoing (40–42; 46–51).

Despite their effectiveness, GnRH antagonists are not first-line treatments due to cost, limited first-line evidence and side effect profiles (especially without add-back).

There are currently no RCTs comparing different GnRH antagonists or dosing regimens. Comparative studies with other hormonal treatments (progestins or combined hormonal contraceptives) or surgery are also lacking [40].

Table 1 summarizes the effects of available GnRH antagonists based on the scientific literature [38,40–53].

Reimbursement criteria

For the symptomatic treatment of endometriosis, in Belgium, only relugolix 40 mg with add-back therapy is currently reimbursed under the following conditions:

> *"Women with a confirmed diagnosis based on imaging (ultrasound/MRI) and/or laparoscopy, who have undergone at least 12 months of hormonal therapy (with or without NSAIDs) for endometriosis which proved insufficiently effective."*

Reimbursement must be requested by a medical specialist. The initial authorization for reimbursement must be requested by the treating gynecologist for a period of 60 weeks. Afterward, it can be renewed in 60-week period. [54]

Table 1
Summary of efficacy and safety of GnRH antagonist use.

GnRH Antagonist	Efficacy	Safety	Available in Belgium for endometriosis indication	Ref
Elagolix 150 mg once daily / 200 mg twice daily	↓ dysmenorrhea and NMPP after 6 months: dose-dependent ↓ dyspareunia only at 200 mg	Dose-dependent side effects: **BMD loss > 1 %**, hot flashes, headache, nausea	No	[34,35]
Linzagolix 75 /100/200 mg	↓ pelvic pain after 12 weeks: dose-dependent ↓ dyschezia and use of analgesics ↑ QoL (EHP−30)	Dose-dependent side effects: **BMD loss > 1 %**, hot flashes, headache, nausea, abdominal pain	Yes (100 and 200 mg)	[38]
Relugolix 10/20/40 mg	↓ NMPP: dose-dependent ↓ pain after 12 weeks ↑ QoL (EHP−30)	Dose-dependent side effects: **BMD loss > 1 %**, hot flashes, headache, heavy or irregular menstrual bleeding	No	[35,38,42, 45–49]
Relugolix + add-back 40 mg + 1 mg estradiol / 0.5 mg norethisterone acetate	↓ dysmenorrhea and NMPP duration-dependent ↓ analgesic use	Favorable tolerance profile. **BMD loss < 1 %**, headache, hot flashes, nasopharyngitis	Yes	[35,38,42, 45–49]

NMPP = Non-menstrual pelvic pain; BMD = Bone mineral density; QoL = Quality of Life, EHP-30 = Endometriosis Health Profile-30: a patient-centered questionnaire to assess health-related quality of life in endometriosis

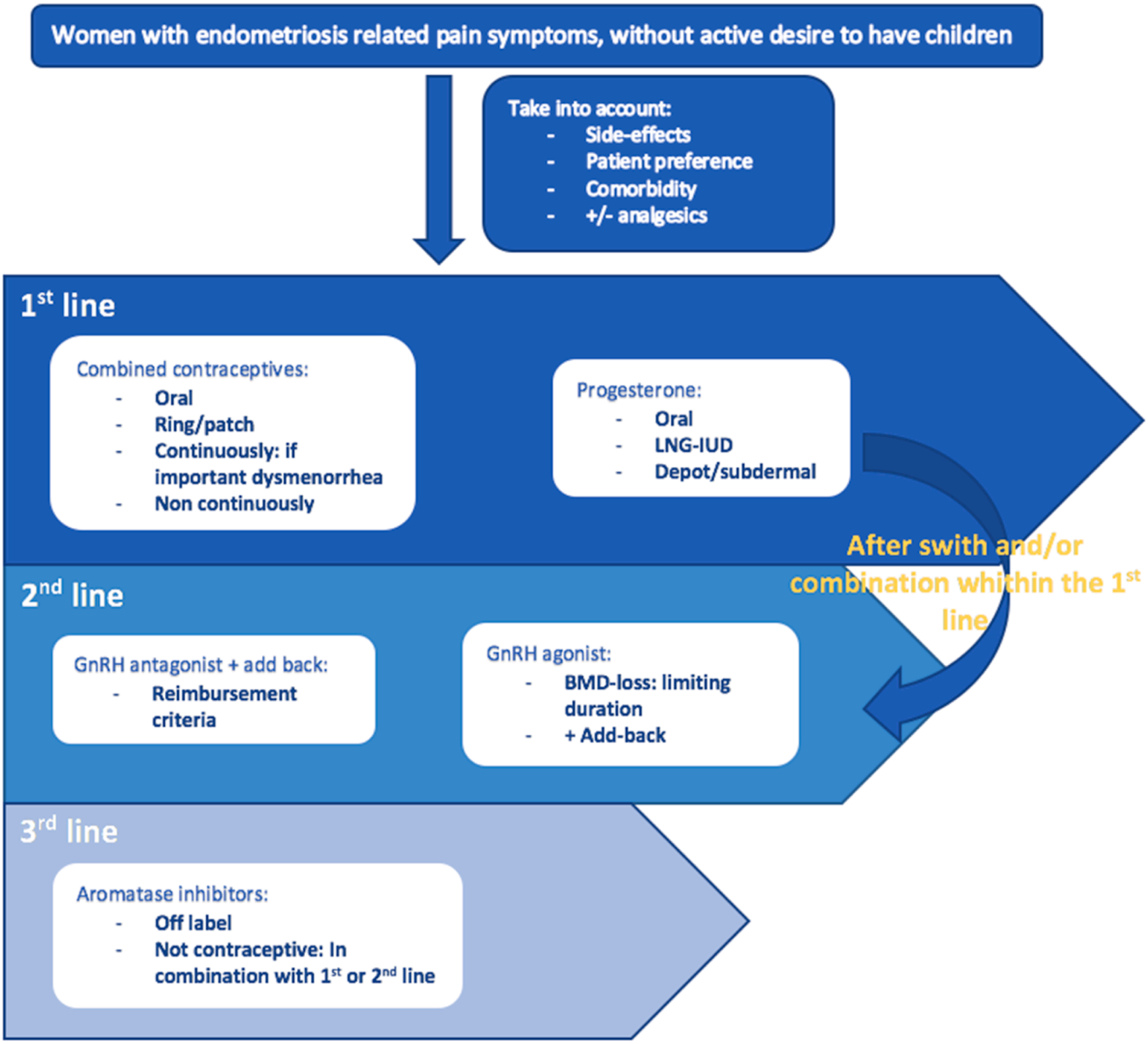

Fig. 1. Flowchart of pharmacological treatment for endometriosis-related pain (according to Flemish clinical practice).

Recommendations

GCP (Good Clinical Practice): The panel recommends that GnRH antagonists be prescribed only as a second-line option (e.g., if hormonal contraceptives or progestins prove ineffective), due to their side effect profile—especially when prescribed without add-back therapy.

Strong for: The panel strongly recommends prescribing GnRH antagonists to women to reduce endometriosis-related pain. There is growing evidence on dosage effectiveness.

Strong: The panel strongly recommends prescribing combined hormonal add-back therapy together with GnRH antagonist therapy to prevent bone loss and hypoestrogenic symptoms.

B5. Aromatase Inhibitors

Effectiveness (recommendation: xxxx; evidence: ++)

The use of aromatase inhibitors, letrozole or anastrozole, for the treatment of endometriosis is considered off-label in Belgium. Both letrozole combined with norethisterone acetate or desogestrel, and anastrozole combined with combined oral contraceptives, lead to a significant reduction in endometriosis-related pain. In particular, NMPP and deep dyspareunia significantly improve after 6 months of treatment with letrozole 2.5 mg/day + norethisterone acetate 2.5 mg/day, with significantly lower pain intensity observed when letrozole is added compared to norethisterone acetate monotherapy. The therapeutic indications remain limited due to the side effect profile of aromatase inhibitors [1,55,56].

Safety

Aromatase inhibitors are primarily associated with hypoestrogenic side effects such as vaginal dryness, hot flashes, and reduced BMD. It should be noted that aromatase inhibitors do not act as contraceptives when used as monotherapy.

Recommendations

Strong for: For women with endometriosis-related pain who do not respond to other medical or surgical treatments, aromatase inhibitors may be prescribed (off-label), as they reduce endometriosis-related pain. They may be used in combination with oral contraceptives, progestins, GnRH agonists, or GnRH antagonists. In premenopausal women, they should only be used in combination with an ovulation-inhibiting agent.

Note: No reimbursement is currently available for the indication of endometriosis.

Non-pharmacological treatment strategies for endometriosis-related pain

There is limited evidence regarding the effectiveness and potential risks of non-pharmacological treatments. Therefore, this is not the focus of this clinical guidance paper. The panel suggests that physicians may discuss non-pharmacological interventions with the patient. However, no specific recommendation can be made for any individual non-pharmacological intervention (such as Chinese medicine, nutrition, electrotherapy, acupuncture, physiotherapy, physical activity, and psychological interventions) for improving pain or quality of life, as the potential benefits or harms remain unclear.

C. Pharmacological prevention of recurrent endometriosis and related pain symptoms

Secondary prevention of endometriosis refers to the prevention of recurrence starting six months after surgery. This differs from immediate postoperative treatment (< 6 months), which focuses on improving short-term outcomes. Recurrence of endometriosis is not uniformly defined in the literature—most often as recurrence of endometriomas, and less frequently as recurrence of endometriosis-related pain symptoms or as indicated by changes in therapy (e.g., reoperation).

Key risk factors include patient-related aspects (such as family history of endometriosis and younger age) and surgery-related factors (such as adhesions and the degree of surgical radicality) [57,58].

Type of pharmacological prevention

Regarding disease recurrence in a broad context, there may be a reduced risk with the use of combined oral contraceptives (COC), progestogens, GnRH agonists, and danazol. A systematic literature review by Zakhari et al. (2021) indicates that COCs are the most effective. The meta-analysis by Chen et al. (2020) shows that long-term use (13–24 months) of COCs and GnRH agonists postoperatively does not provide a clear advantage in preventing pain recurrence compared to no postoperative medical treatment [58,59].

Combined hormonal contraceptives

A systematic literature review by Zakhari et al. (2020) demonstrated that long-term use of COCs, especially with continuous intake, reduces the chance of disease recurrence compared to no treatment (RR 0.32; 95 % CI 0.23–0.44). Only one study examined cyclic use. Long-term use, whether continuous or cyclic (6–24 months), can reduce dysmenorrhea but may have no effect on NMPP or dyspareunia. The duration of treatment determines the duration of the protective effect [58–60].

Progestogens

LNG-IUD

In patients with moderate to severe dysmenorrhea, recurrence of dysmenorrhea is reduced with postoperative use of an LNG-IUD. Studies indicate that the LNG-IUD is as effective in pain reduction as COCs, GnRH agonists and danazol, with significantly higher patient satisfaction compared to COCs. However, compared to GnRH agonists more vaginal bleeding is reported after treatment with LNG-IUD [61–63]. No conclusions can be drawn regarding other types of pain complaints.

Oral Progestogens:

Gestrinone: A subgroup analysis by Zakhari et al. (2021) shows a non-significant reduction in recurrence with the use of gestrinone (2.5 mg twice a week) compared to no treatment [58].

Dydrogesterone: Dydrogesterone 10–20 mg/day from cycle day 5–25, for 3–6 months, can significantly improve NMPP, dysmenorrhea and dyspareunia. Reductions of 95 %, 87 % and 85 % in NMPP, dysmenorrhea, and dyspareunia, respectively, are observed after 6 cycles [64].

Dienogest: Long-term postoperative use of dienogest (24–30 months) results in less recurrence of pain, endometriomas, and rectovaginal lesions. However, the recurrence rate is higher compared to treatment with GnRH agonists [65,66].

To date, no studies have demonstrated a preference for a specific form of progestogen administration for the prevention of recurrence. A review by Liu et al. (2021) indicates that postoperative use of dienogest up to 12 months results in a reduction in the VAS score compared to LNG-IUD. However, these are retrospective studies with small sample sizes, indicating low evidence [67–69].

GnRH Agonists

GnRH agonists show a significant reduction in recurrence compared to no treatment (RR 0.33; 95 % CI 0.51–0.87), but their application is limited by their side effects [58].

Aromatase Inhibitors

Combining LNG-IUD with an aromatase inhibitor such as anastrozole (1 mg/day) yields better results in reducing dyspareunia, dysmenorrhea, and pain scores (VAS) than LNG-IUD alone. The effect is significant after one year of use. Less recurrence of endometriomas is also observed, though not significantly compared to LNG-IUD alone. No difference is noted in the number of reoperations [70].

Prevention by endometriosis subtype

Data on postoperative therapy are not always available by subtype and remain rather scarce.

Ovarian endometriomas

Veth et al. (2024) reported a postoperative recurrence rate of endometriomas of 27 % after 24 months in patients who did not receive hormonal therapy. Recurrence of endometriomas was less common in patients taking combined oral contraceptives (COCs) compared to those not taking them. Continuous intake of COCs appears to be more effective than cyclic intake [70–74]. (recommendation: xxxx; evidence: ++)

Two meta-analyses with similar objectives, conducted by Wattanayingcharoenchai et al. (2020) and Chui-Ching et al. (2022), examined the effectiveness of various hormonal therapies (dienogest, LNG-IUD, and COCs), either as monotherapy or in combination with GnRH agonists, over a six-month period. A reduction in endometrioma recurrence was only observed with treatment durations longer than six months,

regardless of the type of therapy used. Despite similar research aims, the two studies reached different conclusions regarding which therapy is most effective in preventing postoperative recurrence of endometriomas, making it difficult to issue a more specific recommendation [69,75].

Deep Endometriosis

Although available data are limited, prolonged postoperative hormone therapy appears to prevent recurrence of endometriosis-associated symptoms. In women who became pregnant postoperative after shaving of deep endometriosis (DE) and used norethisterone acetate (5 mg once daily) postpartum, a lower recurrence rate of symptoms (2 % vs. 7 %) was observed compared to those who received no medication [73,76]. (recommendation: xxx; evidence: +)

Conclusion

In general, hormonal therapy has a beneficial effect on the postoperative recurrence risk of endometriosis, although most of the evidence comes from studies on endometriomas. Currently, there is no clear evidence that any one hormonal therapy is superior for the secondary prevention of symptoms (particularly dysmenorrhea). Since COCs and progestins are considered first-line treatments, they can be readily prescribed for secondary prevention in patients without an active desire to conceive—taking into account the patient's preferences, costs, availability, risks, and side effects.

Recommendations:

Strong for: For the secondary prevention of endometriosis-related dysmenorrhea, the panel recommends prescribing a levonorgestrel-releasing intrauterine system (52 mg LNG-IUS) or combined hormonal contraceptives for at least 18–24 months postoperatively.

Weak: For the secondary prevention of endometriomas and postoperative symptom recurrence, long-term hormonal treatment should be offered to women who do not wish to become pregnant immediately.

Weak for: To prevent recurrence of deep endometriosis and associated symptoms, long-term postoperative administration of hormonal therapy may be considered.

Quality Control

The quality control of this clinical guidance will be conducted through external review. The preliminary version of the clinical guidance will be available for 4 weeks to VVOG members, during which time they can submit amendments via the VVOG website.

Sponsorship and conflicts of interest

- Dr. Celine Bafort, gynecologist, UZ Leuven:

- Received sponsorship by Gedeon Richter and Ferring Pharmaceuticals to travel and attend scientific meetings

- Dr. Celine Blank:

- Received sponsorship from Gedeon-Richter, Bridea, Erbe, Goodlife, Memidis Pharma B.v., Ferring Pharmaceuticals and Samsung healthcare

- Dr. Brecht Geysenbergh

- Member advisory board Gedeon-Richter
- Received sponsorship from Gedeon-Richter, Theramex, Merck, Ferring and Goodlife

- Dr. Jasper Verguts, gynecologist, Jessa Hospital Hasselt:

- Member national and international advisory board Gedeon Richter
- Received sponsorship form Theramex and Merck.

- Prof. Dr. Carla Tomassetti, gynecologist, UZ Leuven:

- Deputy director of JMIG (paid to institution, no private revenue)
- Received sponsoring by Merck SA for a clinical fellowship programme for reproductive endocrinology (paid to institution, no private revenue), consulting fees from Gedeon Richter and Merck SA (paid to institution, no private revenue), honoraria for lectures/presentations by Gedeon Richter, Merck SA and Ferring Pharmaceutical (paid to institution, no private revenue), sponsoring by Gedeon Richter, Merck SA and Ferring to travel and attend scientific meetings.

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The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.
These conflicts of interest had no impact on the development of this clinical guidance.

Implementation

The final clinical guidance will be published in EJOG, *Gunaïkeia*, the official journal of the VVOG and on the VVOG website.

Suggestions for Future Scientific Research

Currently, there are few (very) long-term studies available for the various hormonal treatments, even though these are intended for prolonged use—both for the symptomatic treatment and for prevention of recurrence after surgery.

There is also a clear need for comparative studies between the various products in terms of effectiveness and side effect profiles, particularly when comparing first-line treatments (e.g., dienogest) to second-line medications (e.g., relugolix with add-back therapy).

GnRH antagonists have only recently been introduced as a treatment option for endometriosis-related pain. Data on relugolix with add-back therapy up to 24 months are already available from the SPIRIT I and SPIRIT II studies, but studies on other GnRH antagonists are still ongoing. The methodology of the available GnRH antagonist studies (specifically the included population and comparison with placebo) positions these medications exclusively as second-line treatments. Other options could be explored. Long-term research, including comparative studies with other treatment options, remains necessary. Additionally, studies should be conducted regarding the potential role of GnRH antagonists in secondary prevention (of recurrence).

Long-term studies on recurrence prevention are needed, with a clear and consistent definition of recurrence in a broad population, as well as comparisons of different therapeutic options and routes of administration.

Given the low level of evidence regarding non-pharmacological treatments, these were not covered in the guidance. Concrete scientific research in this field is strongly recommended.

Limitations

One limitation of this clinical guidance paper is that patient groups were not involved in its development. However, the original ESHRE guideline did involve patient representatives.

Disclaimer

This clinical guidance has been compiled and maintained with the utmost care. Nevertheless, the VVOG accepts no liability for any inaccuracies, nor for any damage, inconvenience, or harm of any kind resulting from actions, omissions, or decisions based on this information.

Members of the Clinical Guidance Panel

Dr. Ellen Remans, resident in gynecology, UZ Leuven
Dr. Celine Bafort, gynecologist, UZ Leuven
Dr. Celine Blank, gynecologist fellow, UZ Leuven and GZA Antwerp
Dr. Alex Bongima, resident in gynecology, UZ Leuven
Dr. Brecht Geysenbergh, gynecologist, GZA Antwerp
Dr. Geert Page, gynecologist, coordinator CG project VVOG
Dr. Tjalina Hamerlynck, gynecologist, UZ Gent
Dr. Jasper Verguts, gynecologist, Jessa Hospital Hasselt
Prof. Dr. Carla Tomassetti, gynecologist, UZ Leuven

Review

The clinical guidance paper will be reviewed in 3 years by the VWAG working group, unless new high-grade evidence becomes available before then.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Dr. Celine Bafort, gynecologist, UZ Leuven:

Received sponsorship by Gedeon Richter and Ferring Pharmaceuticals to travel and attend scientific meetings

Dr. Celine Blank:

Received sponsorship from Gedeon-Richter, Bridea, Erbe, Goodlife, Memidis Pharma B.v., Ferring Pharmaceuticals and Samsung healthcare

Dr. Brecht Geysenbergh

- Member advisory board Gedeon-Richter
- Received sponsorship from Gedeon-Richter, Theramex, Merck, Ferring and Goodlife

Dr. Jasper Verguts, gynecologist, Jessa Hospital Hasselt:

- Member national and international advisory board Gedeon Richter
- Received sponsorship form Theramex and Merck.

Prof. Dr. Carla Tomassetti, gynecologist, UZ Leuven:

- Deputy director of JMIG (paid to institution, no private revenue)
- Received sponsoring by Merck SA for a clinical fellowship programme for reproductive endocrinology (paid to institution, no private revenue), consulting fees from Gedeon Richter and Merck SA (paid to institution, no private revenue), honoraria for lectures/presentations by Gedeon Richter, Merck SA and Ferring Pharmaceutical (paid to institution, no private revenue), sponsoring by Gedeon Richter, Merck SA and Ferring to travel and attend scientific meetings.

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

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Ellen Remans[a], Celine Bafort[a], Celine Blank[a,b], Alex Bongima[a], Brecht Geysenbergh[b], Tjalina Hamerlynck[c], Geert Page[d], Jasper Verguts[e], Carla Tomassetti[a,*]
[a] *UZ Leuven, Herestraat 49, Leuven 3000, Belgium*
[b] *ZAS Augustinus, Oosterveldlaan 24, Wilrijk 2610, Belgium*
[c] *UZ Gent, Corneel Heymanslaan 10, Gent 9000, Belgium*
[d] *Clinical coordinator Clinical Guidance Program VVOG, Belgium*
[e] *Jessa Ziekenhuis Hasselt, Campus Virga Jesse, Stadsomvaart 11, Hasselt 3500, Belgium*

[*] Corresponding author.
E-mail address: info@vvog.be (C. Tomassetti).