REVIEW

The place of gonadotropin-releasing hormone agonists in the management of endometriosis

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Purpose: *This review focuses on the use of the gonadotropin-releasing hormone (GnRH) agonists, a typically marginalized class of drugs, and describes their role in the management of endometriosis, with special interest in 4 regions: Western Europe, Eastern Europe, the Middle East and China.*
Methods: *A consensus meeting on the use of GnRH agonists in the 4 regions was held in Dubai in November 2012, [AUTHOR: please advise: held by whom? by the authors?] based on a review of published regional guidelines for endometriosis. A selective literature search of articles published in the past 5 years that focused on the use of GnRH agonists in endometriosis was also performed.*
Results: *The guidelines place GnRH agonists as a second-line option for the management of pain in deep infiltrating endometriosis and to improve fertility in women planning to undergo in vitro fertilization. Published articles and personal evidence presented at the meeting suggest that surgery for endometriomas should be delayed as long as possible to conserve ovarian function and that GnRH agonist therapy after surgery may reduce their recurrence. However, although add-back therapy is advocated with the use of GnRH agonists, there is no consensus on when this should be started.*
Conclusions: *There are important regional differences in cultural sensitivities to diagnosis and treatment of endometriosis, as well as a diverging approach to surgery. Given the limitations and conflicts in the diagnosis and management of endometriosis, it is essential that the available drugs, including the GnRH agonists, are used in the most appropriate settings.*

Keywords: *Endometriosis, Gonadotropins, Guideline, Infertility, Pelvic pain, Recurrences*

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INTRODUCTION

The diagnosis of endometriosis is typically delayed by many years due to a combination of ignorance (patients and doctors alike believing that the pain is normal), the difficulty in differentiating it from other causes of pelvic and abdominal pain and the need for surgery for a definitive diagnosis. Endometriosis is a complicated and poorly understood condition in which the severity of disease does not correlate with the frequency and severity of symptoms (1, 2) or with long-term conception or recurrence rates (2). Endometriosis can be classified macroscopically as (i) superficial (peritoneal or ovarian) endometriosis, (ii) ovarian endometrioma and (iii) deep infiltrating endometriosis (DIE) (3). There are limited treatment options for endometriosis, and those that are available are often at odds with patients' ultimate wishes in terms of fertility. The surgical approach relies on eradication of the rogue endometrial

tissue, with success assessed by the level of remaining disease after surgery. An alternative approach is to focus on patient-orientated outcomes that make a difference to the daily lives of those affected, such as pain relief and/or pregnancy rates and outcomes (2) and to make management choices based on these needs. This latter approach requires an individualized attitude that takes into account the individual's symptoms and fertility choices.

The consensus is to start with medication before performing surgery. However, surgery is the only possible option to eradicate the condition, even if the risk of recurrence is high, and there are different approaches to deciding when to use a surgical approach, largely dependent on the physician's and surgeon's experience and the patient's age, wish for pregnancy and other preferences.

Increasingly, there is concern about conserving ovarian reserve and the impact of surgery. As the number of available medical therapies is limited, and patient choice is increasingly being sought, it is important that the benefits and limitations of each therapy are clear and that each therapy is used appropriately.

This paper focuses on the treatment of DIE and ovarian endometrioma with a class of drugs that are typically marginalized in the medical management of endometriosis, the gonadotropin-releasing hormone (GnRH) agonists, and seeks to address whether they have a valid role and, if so, what is it and in which patients.

METHODS

Guidelines on endometriosis were identified through a PubMed search. In addition, a selective literature search of articles published in the past 5 years that contained the terms *GnRH agonist, endometriosis* or *endometrioma(s)* was performed.

TRENDS IN THE MANAGEMENT OF ENDOMETRIOSIS

The true prevalence of endometriosis is not known, but the costs associated with its treatment are higher than many other chronic conditions – estimates based on 2002 US data put the global cost of the disease (including analgesics, hormonal therapies, gynecological consultations, hospital admissions, surgical procedures, days off work and reduced productivity) at US $22 billion per year compared with US $865 million for Crohn's disease and US $13 billion to $17 billion for migraine (4, 5). In many countries, reimbursement of some medical options is limited or unavailable, as they are classified as fertility drugs. As suggested by Vercellini et al (5), decision makers should base their decisions on a patient-centered view built on the most up-to-date available evidence, with reimbursement based on the recommendations in national guidelines.

Despite there being hopes for new therapies, the medical options are still very limited, and diagnosis is still dependent on surgical evidence. In the Westernized world, where many women are delaying motherhood and infertility is increasing, there is increasing concern about the preservation of the ovarian reserve and the potentially negative effects of surgery, especially for endometriomas. This is a highly controversial area, with some national guidelines advocating surgery for most patients and others that recommend delaying surgery. In Iran (6) and Russia (7), the guidelines advocate delaying surgery in endometriomas <4 cm, especially in unmarried and nulliparous women or women with low ovarian reserve according to antral follicular count (AFC) and anti-Müllerian hormone (AMH). However, in Russia, surgery for all sizes of endometriomas is recommended when ovarian cancer cannot be excluded; in these situations, experienced surgeons use minimally invasive surgery to maximize preservation of the ovarian reserve (7). In China, surgery is suggested for endometriomas of ≥5 cm (8). In Europe (Royal College of Obstetricians and Gynaecologists [RCOG] and European Society of Human Reproduction and Embryology [ESHRE]), surgery is recommended prior to *in vitro* fertilization (IVF) for endometriomas of ≥4 cm (9, 10) or 6 cm in France (11). In Canada, the threshold is 3 cm (1).

WHAT IS THE PLACE OF GnRH AGONISTS IN THE MANAGEMENT OF ENDOMETRIOSIS?

Current treatment options

The use of combined oral contraceptives (COCs) is considered the first-line treatment for pelvic pain associated with endometriosis, although there are very few randomized controlled trials (RCTs) that compare their use with other medical options (1). The available evidence supports the use of continuous COCs to maintain pain

relief in women with peritoneal and ovarian lesions, whereas a progestin (norethisterone acetate) appears to be the preferred compound in patients with rectovaginal disease (5).

A systematic search of all randomized trials [AUTHOR: please advise: "RCTs"? (i.e., also "controlled"?)]of the use of oral contraceptives (OCs) in the treatment of symptomatic endometriosis (12) revealed only 1 study. This study suggested that the OC pill studied was as effective as a GnRH analogue in treating endometriosis-associated painful symptoms of endometriosis (13). However, the review noted that the lack of studies with larger sample sizes or focusing on other comparable treatments is concerning, and further research is needed (12).

Progestins will "fail" in about a third of women, either through lack of pain relief (13) or due to discontinuation or the need for surgery (5). This may be due to altered, reduced or absent progesterone receptor subtypes in the endometrial tissue (1, 5, 14, 15).

If COCs or progestins do not resolve the pain, second-line options are danazol or GnRH agonists; see Tab. I for a review of current guidelines for the medical treatment for pain. It is important to note that, in most countries, GnRH agonists (with/without add-back therapy) are approved for a maximum period of use of 6 months. This present review reflects the authors' points of view on the appropriate use of GnRH agonists, and individual prescribers are advised to consult their approved indications for GnRH agonists in their country.

Furthermore, the use of danazol, a synthetic steroid hormone, is limited in many countries by its side effect profile. GnRH agonists may be effective by inducing hypoestrogenism and thereby inactivating the endometriotic lesions (see Tab. I for published guidelines and/or recommendations for the medical management of endometriosis). However, use of a GnRH agonist alone results in many unpleasant symptoms associated with estrogen deficiency, such as those typically experienced during the menopause (1, 19).

TABLE I - REVIEW OF CURRENT GUIDELINES FOR THE MEDICAL TREATMENT FOR PAIN ASSOCIATED WITH ENDOMETRIOSIS

Society, date (ref.)	First-line therapy	Second-line therapy	Additional comments
Society of Obstetricians and Gynaecologists of Canada (SOGC), 2010 (1)	• Continuous COCs • Progestin alone (oral, intramuscular or subcutaneous)	A GnRH agonist with add-back therapy (>6 months if combined with add-back therapy from the start of treatment); note that COCs are not suitable for add-back therapy Levonorgestrel intrauterine system	The use of aromatase inhibitors is still experimental
American College of Obstetricians and Gynecologists (ACOG), 2010 (16)	*Suspected endometriosis* • COCs • Empiric treatment with 3 months' GnRH agonist is appropriate and less expensive than laparoscopy *Confirmed endometriosis* • COCs • COCs + depot medroxyprogesterone *Pain due to endometriosis in nonreproductive organs* • GnRH agonists (except in cases of obstruction of the ureter or bowel)	Progestins (oral norethindrone acetate, LNG-IUS, [AUTHOR: please advise: correct edit?] subcutaneous DMPA) Danazol GnRH agonists (prolonged use for up to 1 year if add-back therapy is used)	Although highly effective, danazol has a side effect profile, which includes acne, hirsutism and myalgias, that is more severe than other drugs available Aromatase inhibitors may be used with a progestin or COC

(To be Continued)

TABLE I - CONTINUED

Society, date (ref.)	First-line therapy	Second-line therapy	Additional comments
European Society of Human Reproduction and Embryology (ESHRE), 2013 (9)	*Suspected endometriosis* • COCs (unclear whether the COC should be taken conventionally, continuously or in tricycle regimen) • Progestogens • Levonorgestrel intrauterine system • GnRH agonists *Confirmed endometriosis* • Treatments of confirmed endometriosis with COCs, danazol, gestrinone, medroxyprogesterone acetate and GnRH agonists are equally effective, but their side effect and cost profiles differ • GnRH agonists (for up to 2 years with combined add-back therapy; progestogen as only add-back therapy is not protective)		Guidelines do not define first-line and second-line treatment options Treatment for ≤2 years with estrogen/progestogen add-back is effective and safe for pain relief and bone density protection; progestogen as only add-back is not protective Careful consideration should be given to the use of GnRH agonists in women who may not have reached their maximum bone density
Royal College of Obstetricians and Gynaecologists (RCOG), 2008 (10)	• Treatment with COCs, danazol, gestrinone, medroxyprogesterone acetate and GnRH agonists are equally effective, but their adverse effect and cost profiles differ • GnRH agonist treatment for 3 months may be as effective as 6 months, in terms of pain relief • GnRH agonist treatment for up to 12 months with combined add-back therapy appears to be effective and safe in terms of pain relief and bone mineral density protection • The LNG-IUS appears effective		Guidelines do not define first-line and second-line treatment options Pilot data suggest that the aromatase inhibitor, letrozole, may be effective, although it is associated with significant bone density loss
Collège National des Gynécologues et Obstétriciens Français (CNGOF), 2006 (11)	• Treatment directed at establishing amenorrhea (COCs, continuous monophasic estroprogestins, progestins, danazol or GnRH analogs) is recommended, used according to the protocols outlined by AFSSAPS (French Health Product Safety; 2005) [AUTHOR: please spell out abbreviation and give this reference a number and cite in References.] • Maximum of 1 year of GnRH agonists therapy with add-back therapy if treatment is longer than 3 months		Guidelines do not define first-line and second-line treatment options
German and Austrian Societies for Obstetrics and Gynecology (DGGG and OEGGG), 2013 (17)	• Following hormonal suppression of the ovarian function, endometriotic implants may undergo regression. For the reduction of endometriosis-associated symptoms, progestins, OCs or GnRH analogs may be used to induce therapeutic amenorrhea		There is no mention of the need for add-back therapy to accompany the administration of a GnRH agonist
World Endometriosis Society Montpellier Consortium, 2013 (18)	• Empirical treatment: In some circumstances, second-line medical treatment with GnRH agonists with add-back HRT, or LNG-IUS may be considered for use as empirical medical treatment for women who are not optimally treated with first-line empirical therapy prior to surgical diagnosis and treatment, while awaiting laparoscopic surgery		
	• Medical therapy for women with symptomatic endometriosis: second-line medical treatments could include GnRH agonists (which should be used with add-back HRT, routinely), the LNG-IUS and depot progestins		

All guidelines also include recommendations for analgesia; these are not included in this table. Where the recommendations do not give specific first- and second-line options, the columns have been merged.
COC = combined oral contraceptive; DMPA = ; [AUTHOR: please identify this abbreviation.] GnRH agonist = gonadotrophin-releasing hormone agonist; HRT = hormone replacement therapy; LNG-IUS = levonorgestrel intrauterine system; OC = oral contraceptive.

To avoid these symptoms, including loss of bone mineral density which may be difficult or impossible to reverse (19), GnRH agonists should be used with add-back hormonal therapy at the start of treatment (1,19).

The role of GnRH agonists in reducing preoperative pain

A systematic search of MEDLINE from 1964 to July 2006 yielded 21 RCTs and 1 cohort study that compared the efficacy of GnRH analogues and danazol. No overall significant differences were found after 6 months of treatment between the groups (overall pain, pelvic pain, dyspareunia, pelvic tenderness, pelvic induration or symptom relief) (20) (see Tab. II). Similarly, there were no significant differences between GnRH agonists and danazol after 1 year of treatment in overall pain, dysmenorrhea, pelvic pain, dyspareunia, pelvic tenderness or pelvic induration (20).

A subsequent meta-analysis of the 4 RCTs that recorded symptom relief rates after 6 months of treatment concluded that GnRH analogues were more effective than danazol (odds ratio [OR] = 2.0019; 95% confidence interval [95% CI], 1.0471-3.8272) (14). However, danazol can only be administered in low doses due to its side effects (including weight gain, acne, hirsutism, breast atrophy and dyslipidemia); its use has been discontinued in many countries.

In the same review, it was concluded that there were insufficient data to compare the effectiveness of OCs with GnRH agonists and danazol; although the only RCT that compared OCs with GnRH analogues (6-month consecutive treatment with each) reported that they were similarly effective for the relief of symptoms associated with endometriosis (20).

A Japanese study reported that treatment with a GnRH agonist markedly reduced the inflammatory reaction and angiogenesis and significantly induced apoptosis in tissues derived from women with endometriosis, adenomyosis and uterine myoma, suggesting that GnRH agonist therapy might have multiple local biological effects that are involved in disease regression and subsequent resolution of symptoms (31).

Anxiety and depression are present in a large majority of patients (85%) with endometriosis, and GnRH agonists are reportedly associated with anxiety and depression in patients during treatment. In the first study of its kind, the use of progressive muscle relaxation (PMR) has been shown to be effective in improving anxiety, depression and quality of life of endometriosis patients undergoing GnRH agonist therapy (32).

Role of GnRH agonists in delaying time to pain recurrence postoperatively

Several studies have compared GnRH agonists with placebo or expectant management for delaying the recurrence of pain after surgery (Tab. III). Results have been mixed: some studies reported reduced pain compared with placebo (34) or expectant management (37), while others reported no difference compared with placebo (33, 38), expectant management with placebo (35) or expectant management (36, 39) or compared with an aromatase inhibitor, letrozole (38). Most of the studies included moderate to severe endometriosis patients.

Role of GnRH agonists in reducing recurrence of endometriomas

There is increasing evidence that some degree of normal ovarian tissue is excised together with the endometrioma wall during laparoscopic cystectomy for endometriomas, resulting in a low ovarian reserve (40-42). Ovarian surgery in endometriosis patients should always be performed by experienced surgeons, and there is a growing argument that, where possible, surgery should be avoided or delayed in order to both preserve and improve fertility (40, 43).

Treatment with a GnRH agonist for 6 months has been demonstrated to have a beneficial impact on the recurrence rate after conservative laparoscopic surgery for ovarian endometriomas: lower cumulative probabilities of disease recurrence were reported for 3 months or 6 months of GnRH treatment (3.4% and 0, respectively) [AUTHOR: please advise: correct edit?] compared with 5.4% for expectant management (39). The authors concluded that longer term treatment with a GnRH agonist (>6 months) would be beneficial in reducing objective disease recurrence and/or pain recurrence (39).

The combination of GnRH agonist therapy with transvaginal ultrasound-guided cyst aspiration, a simple and non-invasive procedure that removes cyst without affecting ovarian function, further improves the therapeutic effects and pregnancy outcomes in infertile patients with ovarian endometriosis who undergo IVF (44).

Role of GnRH agonist as an alternative to surgery in specific cases

Anecdotal evidence suggests that GnRH agonists may be an effective alternative to surgery in younger women with DIE and no immediate desire to start a family, and in

TABLE II - RCTS COMPARING GnRH AGONISTS WITH PLACEBO, OCS OR DANAZOL FOR THE TREATMENT OF PAIN ASSOCIATED WITH ENDOMETRIOSIS

Author (year) (ref.)	No. GnRH agonist/ control (comparator) [AUTHOR: please advise: correct edit?]	Diagnosis	Measurement parameter	Results (therapy vs. control)
Ling (1999) (21)	50/50 (placebo)	Clinically suspected endometriosis	Three months posttherapy change in 10-point pain scale value	-7.4 vs. -1.6*
Fedele (1993) (22)	19/16 (placebo)	Minimal-mild endometriosis	Dysmenorrhea rate at 3 months Dysmenorrhea rate at 12 months	27% vs. 81%* 47.5% vs. 81%*
Bergqvist (1998) (23)	24/25 (placebo)	Minimal-severe endometriosis	Posttherapy change in 3-point pain scale value	-2.85 vs. -0.33*
Dlugi (1990) (24)	32/31 (placebo)	Minimal-severe endometriosis	1 year post-therapy change in 3-point pain scale value	-2.2 vs. -0.2*
Miller (1990) (25)	28/20 (placebo)	Unclassified endometriosis	Symptom relief rate	Not described*[AUTHOR: please advise: significant but not described?]
Vercellini (1993) (26)	28/29 (oral contraceptive)	Moderate or severe pelvic pain and laparoscopically diagnosed endometriosis	Six month posttherapy change in 10-point pain scale value	7.5 ± 2.5 vs. 7.4 ± 1.7†
Australian/New Zealand Zoladex Study Group (1996) (27)	(danazol)	Symptomatic and/or infertility associated endometriosis	Symptoms relieved Symptoms not relieved	26 vs. 20 1 vs. 8
Kennedy (1990) (28)	50 vs. 23 (danazol)	Symptoms of pelvic pain, dyspareunia, dysmenorrhea or infertility, with severity assessed laparoscopically	Complete symptom relief Symptoms unchanged	29/50 (58%) vs. 14/23 (61%) 3/50 (6%) vs. 3/23 (13%)
Henzl (1990 – study I) (29)	70 (800 mg), 73 (400 mg)/70 (danazol)	Laparoscopically confirmed endometriosis	Complete symptom relief Partial symptom relief No change	72/143 vs. 34/70 60/143 vs. 29/70 5/143 vs. 3/70
Henzl (1990 – study II) (29)	104/63 (danazol)	Laparoscopically confirmed endometriosis	Complete symptom relief Partial symptom relief	59/104 vs. 30/63 40/104 vs. 29/63
Adamson (1994) (30)	45 (800 mg) vs. 34 (danazol)	Laparoscopically confirmed pelvic endometriosis and dysmenorrhea, dyspareunia or pelvic pain	Pain-free 6 months after treatment	96% vs. 94%

Only danazol studies in which symptom relief was measured have been included here; data taken from a full review of comparative studies of danazol vs. GnRH agonists (14).
GnRH agonist = gonadotrophin-releasing hormone agonist; OCs = oral contraceptives; RCT = randomized controlled trial.
*Significant difference; †no significant difference; ‡not defined. [Au: Please define ‡ in the table data (missing)]

TABLE III - STUDIES COMPARING GnRH AGONISTS WITH PLACEBO OR EXPECTANT MANAGEMENT AFTER SURGERY FOR ENDOMETRIOSIS

Author (year) (ref.)	No. GnRH agonist/ control (comparator) [AUTHOR: please advise: correct edit?]	Diagnosis	Measurement parameter	Results (therapy vs. control)
Parazzini (1994) (33)	36/39 (placebo)	Moderate-severe endometriosis	Nine month posttherapy change in 10-point pain scale value after 3 months of treatment	-7.0 ± 4.1 vs. -6.9 ± 4.6†
Hornstein (1997) (34)	56/53 (placebo)	Moderate-severe endometriosis	Rate at which an alternative therapy was required after 3-month treatment	31% vs. 57%*
			Time until alternative therapy was required after 3-month treatment	>24 vs. 11.7 months*
			Posttherapy change in 3-point pain scale value after 3-month treatment	-3.2 ± 2.7 vs. -1.0 ± 2.3‡
			Six month posttherapy change in 3-point pain scale value after 3-month treatment	-1.5 ± 2.7 vs. -1.1 ± 2.6‡
Loverro (2008) (35)	19/16 (placebo)	Stage III/IV endometriosis	Objective disease recurrence rate after 3 months of treatment, by gynecologic examination and/or pelvic ultrasonography	4 vs. 2
Busacca (2001) (36)	44/45 (expectant management)	Moderate-severe endometriosis	Recurrence rate during follow-up after 3 months of treatment	23% vs. 24%ns
			Recurrence rate 18 months posttreatment after 3-month treatment	23% vs. 29%†
Vercellini (1999) (37)	133/134 (expectant management)	Minimal-severe endometriosis	Recurrence rate 1 year after 3-month treatment	13.1% vs. 21.4%†
			Recurrence rate 2 years after 3-month treatment	23.5% vs. 36.5%†
			Time to recurrence according to survival analysis	$X^2 = 4.19$ (therapy>control)
Alborzi (2011) (38)	Triptorelin (n = 40)/letrozole (n = 47)/control (n = 57) [AUTHOR: please advise: correct edit?]	Endometriosis treated laparoscopically	Recurrence rate of endometriosis at least 12 months after restoration of their regular cycle	5% vs. 6.4% vs. 5.3% (no significant difference)

Data taken from a full review of the management of pain associated with endometriosis (14).
*Significant difference; †No significant difference; ‡Not defined.

older women who have already had several recurrences or are contraindicated for surgery. In Iran, this potential use is included in the guidelines (6).

Role of GnRH agonist therapy as a "primer" for treatment with oral contraceptives

Postoperative treatment with a GnRH agonist followed by a cyclic OC has been shown to effectively reduce endometrioma recurrence in reproductive-age women who do not want to conceive in the near future (45). To our knowledge, there is no other evidence to support the use of a GnRH agonist to reduce inflammation and increase the efficacy of subsequent treatment with OCs, although this is a logical hypothesis and one that is used in China (where 3-6 doses of GnRH agonist are followed by an OC).

Role of GnRH agonists in improving fertility rates pre-IVF

Patients with endometriosis and infertility who are to undergo IVF may benefit from pretreatment with hormonal

suppressants (1): see Tab. IV for published guidelines and recommendations for medical therapies that may be used alongside IVF.

Several studies suggest that women with chronic or advanced endometriosis may benefit from treatment with a GnRH agonist before an IVF cycle (42, 46) (Tab. IV). A Cochrane review identified 3 RCTs involving 165 women treated with IVF for infertility related to endometriosis (46). The clinical pregnancy rate per woman was significantly higher in those receiving GnRH agonist down-regulation for 3-6 months before IVF than in the control group (OR = 4.28; 95% CI, 2.0-9.15). The live birth rate per woman was significantly higher in women receiving the GnRH agonist compared with the control group, in the 1 trial that reported "viable pregnancy" (46). A later study demonstrated no effect on pregnancy rate after 2 months of treatment with

TABLE IV - REVIEW OF CURRENT GUIDELINES FOR THE MEDICAL TREATMENT OF INFERTILITY ASSOCIATED WITH ENDOMETRIOSIS

Society (year) (ref.)	Recommendations/Comments
Society of Obstetricians and Gynaecologists of Canada (SOGC), 2010 (1)	If a patient with known endometriosis is to undergo *in vitro* fertilization (IVF), GnRH agonist suppression with hormone therapy add-back for 3 to 6 months before IVF is associated with an improved pregnancy rate Clinical tip: 3 months of suppression with a GnRH agonist and add-back therapy before IVF in women who have pelvic pain and infertility associated with endometriosis will greatly improve quality of life and reduce discomfort during ovarian stimulation and oocyte retrieval
American College of Obstetricians and Gynecologists (ACOG), 2010 (16)	No specific mention in latest version of guidelines
European Society of Human Reproduction and Embryology (ESHRE), 2013 (9)	Treatment with a GnRH agonist for 3-6 months before IVF or intracytoplasmic sperm injection (ICSI) increases the odds of clinical pregnancy fourfold Controlled ovarian hyperstimulation for IVF/ICSI is equally effective with both GnRH antagonist and GnRH agonist protocols in terms of implantation and clinical pregnancy rates, but COH with GnRH agonists may be preferred because of the availability of more MII oocytes and embryos
Royal College of Obstetricians and Gynaecologists (RCOG), 2008 (10)	Treatment with a GnRH agonist for 3-6 months before IVF in women with endometriosis increases the rate of clinical pregnancy Three randomized controlled trials were identified involving women with endometriosis who were treated with a standard protocol or a GnRH agonist for 3-6 months before IVF; the clinical pregnancy rate per woman was significantly higher (odds ratio = 4.28, 95% confidence interval, 2.00-9.15) in women receiving a GnRH agonist compared with controls
Collège National des Gynécologues et Obstétriciens Français (CNGOF), 2006 (11)	No specific recommendations
Australasian CREI Consensus Expert Panel on Trial (ACCEPT), 2012 (39)	GnRH agonists before IVF
German and Austrian Societies for Obstetrics and Gynecology (DGGG and OEGGG), 2013 (17)	Postoperative treatment with GnRH analogs was ineffective in improving spontaneous pregnancy rates and is, therefore, not recommended
World Endometriosis Society Montpellier Consortium, 2013 (18)	Adjuncts to assisted conception for infertility in women with endometriosis • There is insufficient evidence of benefit of treatment with GnRH agonists before intrauterine insemination (IUI) • GnRH agonists administered for 3-6 months prior to IVF/ICSI in women with endometriosis increase the clinical pregnancy rate • There are no data to compare the approach of pretreatment with the combined OCP versus GnRH agonists

COH = ; [AUTHOR: please identify this abbreviation.] GnRH = gonadotropin-releasing hormone; MII = ; OCP = . [AUTHOR: please identify these abbreviations.]

either a GnRH agonist (triptorelin) or an aromatase inhibitor (letrozole) in 144 infertile women treated laparoscopically for endometriosis; however, there is no information available regarding whether pregnancy was natural or assisted (38).
However, both the European Society of Human Reproduction and Embryology (ESHRE) (9) and Royal College of Obstetricians and Gynaecologists (RCOG) (10) guidelines highlight the fact that the recommendation to use GnRH agonists pre-IVF is based on only 1 properly randomized study and that there is a need for further research into this treatment option, particularly regarding the mechanism of action (9, 10).

Role of add-back therapy with GnRH agonists

The use of add-back therapy is recommended to maintain the therapeutic effects, while ameliorating the potential adverse effects, of GnRH agonist treatment (11, 48-50).
Add-back therapy is based on the hypothesis that there is a threshold serum estrogen concentration that is low enough to prevent endometriosis but high enough to avoid hypoestrogenic symptoms (48). The immediate use of add-back therapy is advocated by the Canadian (1) and Russian guidelines (7) and by several studies (11, 50, 51); American Congress of Obstetricians and Gynecologists (ACOG) guidelines state that add-back therapy "can be" started immediately with the GnRH agonist but do not advocate immediate use (16). The Chinese guidelines recommend the addition of add-back therapy from the second month of GnRH agonist administration (8); the French guidelines, written in 2006 (11), recommend the use of add-back therapy after 3 months and the Iranian guidelines (6) state that add-back therapy is required after 6 months of GnRH treatment. Although the ESHRE and RCOG guidelines state that long-term use of GnRH agonists is possible with concomitant add-back therapy, neither states when that add-back therapy should start (9, 10).
Although not included in the recommendations of the Society of Obstetricians and Gynaecologists of Canada (SOGC), empiric GnRH agonist therapy with add-back therapy is reserved, according to the SOGC, for adolescents over the age of 18 years, owing to concern regarding detrimental effects on bone mineral density (1). Studies have shown that GnRH agonists plus add-back therapy provide effective symptom relief and maintain bone health in adolescents younger than 18 years; however, monitoring of bone mineral density is critical, and prospective studies are needed in this patient population (51, 52).

CONCLUSION: CAN GnRH AGONISTS IMPROVE THE MANAGEMENT OF ENDOMETRIOSIS?

For a condition for which there are relatively few medical treatments, as well as a growing concern over the effect of surgery on ovarian reserve, increasingly restricted health care budgets and a focus on individualized therapy, it is vital that best practice is shared across cultures and borders. Although there are a number of national and regional guidelines, there is still a lack of worldwide consensus on the most appropriate medical and surgical strategies.
As treatment choice depends on the age and life choices of the patient regarding fertility, it is essential that accurate, comprehensive and easy-to-understand information about the condition and treatment options is readily available for parents, nurses and primary care physicians. Although the cost of GnRH agonists and combined add-back therapy is an important consideration, we conclude, based on the available data, that GnRH agonists have an important role to play in the management of certain patients with endometriosis, including:

- Some women with DIE, and as second-line therapy for patients in whom COCs and progestins have not resolved endometriotic pain (including those who wish to avoid or delay surgery and who have no immediate desire to become pregnant);
- To improve fertility in women who are scheduled for IVF;
- Possibly to reduce the recurrence of endometriomas following surgery.

In most countries, GnRH agonists (with/without add-back therapy) are approved for a maximum period of use of 6 months. It is our opinion that the immediate use of add-back therapy in all patient types is important to prevent the side effects usually associated with GnRH agonists.

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