Review Article

Use of GnRH analogue in the endometriosis recurrence after surgery

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Abstract: Endometriosis recurrence after surgery is still an issue that afflicts the gynecologist. Adjuvant hormonal treatments have been suggested and approved in order to delay recurrence in symptoms and endometriotic lesions. The current review analyzes the impact of postoperative gonadotropin-releasing hormone agonists administration on the recurrence rate of endometriosis. We selected randomized controlled trials on this topic. The reported findings are controversial and the definition of recurrence varies among the sources. The emerging results report that the postoperative administration of gonadotropin-releasing hormone agonists seems beneficial on symptoms control and it delays the subjective recurrence (although it is related to the known side effects), but the duration of the post-operative treatment plays an important role.

Keywords: Endometriosis recurrence; gonadotropin-releasing hormone agonist; adjuvant therapy; pain recurrence; chronic pelvic pain

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Introduction

Endometriosis recurrence represents a fight for the gynecologist. The recurrence rate after surgery varies considerably in scientific literature due to multiple factors. Firstly, the definition of the recurrence is different among the available studies. Some studies consider "recurrence" the symptoms reported by patients, while others measure the recurrence with more objective clinical/instrumental methods, for instance, the assessment of endometriomas relapse by ultrasonography. Moreover, the length of follow-up varies among the sources, the previous surgical radicality and technique are different (1).

The general reported incidence rate of disease recurrence, regardless of the definition, is 19.1% after two years from surgical treatment and it ranges between 20% and 44% after five years (1-3). The subjective recurrence seems more frequent than the objective one and there is a low correlation between the symptoms and the stage of the disease. The objective rate is reported to be 9% after three years post-surgery and 28% after 5 years, while the symptoms recurrence varies between 20.5% after 3 years and 43.5% after 5 years (2).

Several mechanisms have been proposed to explain the return of the disease after surgery: the *de novo* recurrence of the endometriotic lesions (probably due to a retrograde menstruation) or the increasing of microscopic lesions persisting after surgery. The frequent relapse of the lesions on the same site of the previous surgical excision supports the last theory (4). Moreover, sometimes surgery is performed in a sub-optimal way, thus leaving on-site small lumps (5).

The adjuvant hormonal treatment is suggested

by numerous evidences and by the guidelines from the European Society of Human Reproduction and Embryology (ESHRE) (6) in order to delay and prevent the recurrence of the disease after surgery and eradicate potential persistent spots of endometriosis. The medical treatment is reported to be more effective when started soon after surgery and when the duration of the treatment itself is long, since exogenous hormones are not healing but they exert a temporary suppressive action on a chronic and estrogen-dependent disease.

Short term treatment, inferior to six months, aims to symptoms control and to delay of the pain return, while a long-term treatment represents a long-term prevention of the disease, ideally avoiding his progression and the related symptoms, such as dysmenorrhea, chronic pelvic pain and deep dyspareunia (7).

However, compared to the short-term therapies, the long-term ones are burdened by more side effects, especially relevant for gonadotropin-releasing hormone agonist (GnRHa) and the danazol, and by costs (particularly for GnRHa and the aromatase inhibitors, AI). An add-back therapy is often administrated in association with GnRHa in order to improve the medications tolerability and the combination AI-GnRHa has been proposed too (8-12). On the other hand, the suspension of the suppressive therapy is associated to a return of the symptoms (13).

The aim of the present review is to assess the effectiveness of GnRHa after surgery for endometriosis in preventing the disease recurrence.

Materials and methods

Study selection and data extraction

We searched for studies evaluating the impact of GnRHa on the endometriosis recurrence. The searches were systematically conducted by two authors through PubMed, Embase, Medline, and Cochrane Library employing several key words: “endometriosis recurrence”, “gonadotropin-releasing hormone agonist”, “adjuvant therapy”, “pain recurrence”, “chronic pelvic pain” and “randomized controlled trial”. Moreover, a manual search was performed using the references cited in reviews and meta-analysis focused on the topic to identify further eligible studies.

We included only high quality randomized controlled trial (RCT) published in English and we collected studies in which the intervention was the GnRHa administration after surgery for endometriosis with the aim of assessing the recurrence rate.

The studies were excluded if the Jadad score was inferior to 3 (see *Table S1*), the study did not specify the recurrence rate after adjuvant therapy, the population did not undergo to a surgical treatment (some researchers performed only a diagnostic laparoscopy before hormonal therapy), the medical intervention was not postoperative and it was not specified which type of hormonal therapy was administered.

Assessment of study quality

Bias of each eligible study was assessed according to the Jadad scale (14) (*Table S1*), evaluating the randomization, the double blinding and the dropout and withdrawal reports of the trials. A score ranging between 3 and 5 was needed to design a trial as “high quality”.

Results

Literature search results

As showed in *Figure 1*, we identified 1747 studies, of which 402 were screened for eligibility. Finally, among the 30 eligible studies, 20 were excluded because they did not satisfy the inclusion criteria (15-34) and a total of 10 relevant RCT were included in the review (35-44).

Evaluation of included studies

We divided the included trials into three subgroups according to the recurrence parameter considered, as summarized in *Tables 1-3*. Three studies (35,41,42) reported an objective parameter of recurrence. They analyzed the rate of endometrioma relapse with an ultrasound exam or the endometriosis recurrence with a second line surgery (sometimes obtaining a histological exam) and/or with an increase of Ca125 serum levels. Four RCT (38,39,43,44) described a subjective recurrence parameter consisting in the severity of pain reported by the patients. Validate pain scales, such as verbal rating scale (VRS) or visual analogue scale (VAS), were employed for measuring the intensity of dysmenorrhea, chronic pelvic pain and dyspareunia. The remaining studies (36,37,40) considered both the subjective and objective recurrence.

The intervention of all the trials consisted by a short-term adjuvant therapy with a maximum treatment duration of 6 months.

Some of the included studies compared GnRHa to other

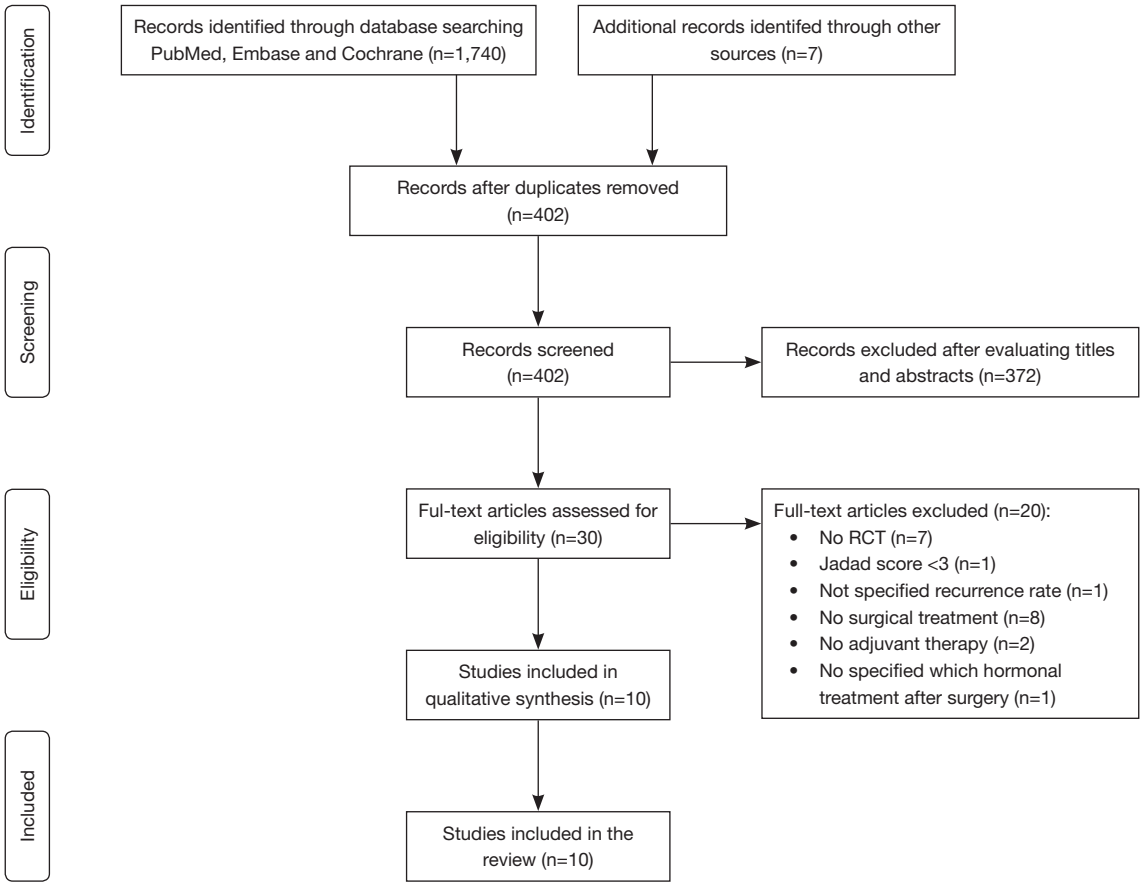

Figure 1 PRISMA flow diagram.

Table 1 Summary of the studies that considered an objective parameter of recurrence

Studies (all RCT)	Participants and intervention	Recurrence parameter	Follow up period and recurrence rate
Shaw *et al.* (2001)	Total n=48	Endometrioma relapse (USG + histology-second-line surgery with excision of the cyst)	6 months FU:
	Goserelin group (3.6 mg subcutaneous injections monthly for 3 months) n=21		Goserelin group 10%
	Control group n=27		Control group 15%
Acien *et al.* (2002)	Total n=52	Recurrence of endometriosis (USG + histology-LPS second-look) + increased serum CA125 levels	24–36 months FU:
	Decapeptyl group (3.6 mg subcutaneous injections monthly for 6 months) n=26		Decapeptyl group 26.9%
	Control group n=26		Control group 30.8%
Sesti *et al.* (2009)	Total n=259	Endometrioma relapse (USG + second-look LPS)	18 months FU:
	Tryptorelin/Leuprorelin group (3.6 mg subcutaneous injections monthly for 6 months) n=65		Triptorelin/Leuprorelin group 10.3%
	Continuous OC group n=64		OC group 15%
	Placebo group n=65		Placebo group 16.6%
	Diet n=65		Diet group 17.8%

RCT, randomized controlled trial; USG, ultrasonography; FU, follow up; LPS, laparoscopy.

Table 2 Summary of the studies that considered symptomatology as recurrence parameter

Studies (all RCT)	Participants and intervention	Recurrence parameter	Follow up period and recurrence rate
Hornstein *et al.* (1997)	Total n=201	Patient-reported pain scores from baseline after surgery	24 months FU:
	Nafarelin group (200 pg intranasal twice daily for 6 months) n=49		Nafarelin group 25%
	Placebo group n=44		Placebo group 47% (P=0.015)
			Needed alternative therapy:
			Nafarelin group 31%
			Placebo group 57% (P<0.001)
Vercellini *et al.* (1999)	Total n=269	VRS ≥5 (dysmenorrhoea, nonmenstrual pain, deep dyspareunia)	12 months FU:
	Goserelin group (3.6 mg subcutaneous injections monthly for 6 months) n=133		Goserelin group 13.1%
	Control group n=134		Control group 21.4% (P=0.143)
			24 months FU:
			Goserelin group 23.5
			Control group 36.5 (P=0.082)
Soysal *et al.* (2004)	Total n=80	Biberoglu and Behrman scale for dysmenorrhoea, dyspareunia and pelvic pain Total Pelvic Symptom Score	24 months FU:
	Anastrozole (1 mg/day) + goserelin group (3.6 mg subcutaneous injections monthly for 6 months) n=40		Anastrozole + goserelin group 45.3%
	Placebo+ goserelin group (3.6 mg subcutaneous injections monthly for 6 months) n=40		Placebo + goserelin group 89.6%
Granese *et al.* (2015)	Total n=78	Pain recurrence (VAS for dysmenorrhea, dyspareunia and non-menstrual pelvic) + Endometriosis Health Profile questionnaire	9 months FU:
	OC group n=39		OC group 10.8%
	Leuprorelin/other GnRHa group (3.6 mg subcutaneous injections monthly for 6 months) n=39		Leuprorelin/other GnRHa group 13.7%

RCT, randomized controlled trial; FU, follow up; VRS, verbal rating scale; VAS, visual analogue scale

hormonal therapies, of which two trials compared GnRHa to OC (38,41) and two others studied the impact of AI (36,43). Both the studies comprising OC group showed similar results concerning the recurrence rate compared to the GnRHa administration. One of them considered the endometrioma relapse (41) and the other one the symptoms recurrence (38). Concerning the AI effectiveness, the two mentioned studies described controversial results. Soysal *et al.* (43) reported a lower recurrence rate with the combination anastrozole-goserelin compared to the goserelin alone after 6 months of treatment, while Alborzi *et al.* (36) did not show any significant difference between triptorelin, letrozole and control group but the duration of the treatment was only 2 months for each group.

The remaining studies include in the present review showed conflicting results too. Three trials did not support the adjuvant GnRHa treatment (35,37,40) and other three reported a positive outcome on recurrence rate (39,42,44). Among the last cited, Vercellini *et al.* and Hornstein *et al.* (39,44) observed an increased pain-free interval and a delay of symptoms needing further treatment after GnRHa administration for 6 months after surgery, compared to no adjuvant treatment. Other researchers (42) reported their outcomes after laparoscopic aspiration of endometriomas, reporting a potential benefit of goserelin administration on diameter of the recurrent endometrioma. A smaller

Table 3 Summary of the studies that considered both symptomatology and objective disease as recurrence parameter

Studies (all RCT)	Participants and intervention	Recurrence parameter	Follow up period and recurrence rate
Busacca *et al.* (2001)	Total n=89	Linear scale for dysmenorrhoea, pelvic pain, deep dyspareunia Multidimensional scale (limitation of daily activities, systemic symptoms, analgesics use) Biberoglu and Behrman scale (dyspareunia)	Median 19, range 6–36 months FU:
	Leuprorelin group (3.6 mg subcutaneous injections monthly for 3 months) n=44		Leuprolide group: Pain 23%; Objective disease 9%
	Control group n=43	Objective disease recurrence (USG)	Control group: Pain 29%; Objective disease 9%
Loverro *et al.* (2008)	Total n=60	Pain recurrence (VRS for dysmenorrhoea, pelvic pain, deep dyspareunia) + endometrioma relapse (USG) + increased serum CA125 levels	60 months FU
	Triptorelin group (3.6 mg subcutaneous injections monthly for 3 months) n=29		Triptorelin group: Pain 44.8%; Endometrioma 21%
	Placebo group n=25		Placebo group: Pain 48%; Endometrioma 17.1%
Alborzi *et al.* (2010)	Total n=144	Endometrioma relapse (USG) + pain recurrence (VAS for dysmenorrhea, dyspareunia and pelvic pain)	≥12 months FU:
	Letrozole group n=47		Letrozole group 6.4%
	Triptorelin group (3.6 mg subcutaneous injections monthly for 2 months) n=40		Triptorelin group 5%
	Control group n=57		Control group 5.3%

RCT, randomized controlled trial; FU, follow up; VRS, verbal rating scale; USG, ultrasonography; VAS, visual analogue scale.

endometrioma size could offer an advantage for a second-line surgery.

Discussion

The use of the post-operative hormonal treatment after conservative or radical surgery for endometriosis is supported by numerous studies and by the ESHRE (6,10). Moreover, treatment duration seems to be crucial in the prevention of the disease (13,45).

The short-term treatment with GnRHa showed conflicting results. However, also OC short term treatment reported similar outcomes to GnRHa treatment concerning the recurrence rate (38,41). Muzii *et al.* (46) showed a low protective effect after adjuvant short term therapy with cyclic OC (although they reported a delay in symptoms recurrence compared to the control group), while other researchers (47-51) reported a beneficial impact of long term OC administration (for more than 6 months). Considering the available literature, it results reasonable to focus our attention on the treatment duration rather than on the kind of suppressive therapy used.

Considering that GnRHa are burdened by the well-known side effects related to hypoestrogenism, the reported studies did not employ them in a long-term period. When they are used for more than 6 months, an add back therapy should be considered. Although it is difficult to understand how much a short-term use of GnRHa influences the recurrence rate, more studies reported a longer pain free interval and a delay of recurrent endometriosis related symptoms.

Finally, we used the Jadad scale to assess potential bias of the studies. This quality scoring system includes the double-blinding among the "quality parameters"; however, most of the RCT are not double-blind (35-38,42,44) because it results difficult to conduct a double-blind study employing a medication with severe side effects.

Conclusions

Long term therapy plays a crucial role in the prevention of endometriosis related symptoms and endometriomas relapse after surgical treatment. However, the well-known side effects caused by GnRHa limit their use for a long period. The review reports conflicting results concerning the role of short-term therapy with GnRHa on recurrence

rate, even if several studies describe a delay of recurrence of symptoms. Further researches are needed to clarify the impact of postoperative suppressive therapy also on deep infiltrating endometriosis (7).

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Quality assessment of the studies according to Jadad scale

RCT	Randomization present*	Blinding present*	Withdrawals and dropouts*	Appropriate randomization**	Appropriate blinding method**	Total score***
Hornstein *et al.* (1997)	1	1	1	1	0	4
Vercellini *et al.* (1999)	1	0	1	1	0	3
Busacca *et al.* (2001)	1	0	1	1	0	3
Shaw *et al.* (2001)	1	0	1	1	0	3
Acien *et al.* (2002)	1	0	1	1	0	3
Soysal *et al.* (2004)	1	1	1	1	0	4
Loverro *et al.* (2008)	1	1	1	1	-1	3
Sesti *et al.* (2009)	1	1	1	1	0	4
Alborzi *et al.* (2010)	1	0	1	1	0	3
Mettler *et al.* (2014)	1	0	1	0	0	2 (excluded)
Granese *et al.* (2015)	1	0	1	1	0	3

*A study receives a score of 1 for "yes" and 0 for "no". **A study receives a score of 1 if the method is described and appropriate, –1 if the method is described but inappropriate, and 0 if no description is given. ***Score range 0-5. Poor quality <3. RCT, randomized controlled trial.