Review Article

A narrative review of using GnRH analogues to reduce endometriosis recurrence after surgery: a double-edged sword

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Background and Objective: Gonadotropin-releasing hormone (GnRH) analogues, including both agonists and antagonists, are a second line therapy for treating endometriosis. They work by down-regulating the hypothalamic-pituitary-gonadal axis, suppressing ovulation and reducing estrogen levels. GnRH analogues are effective, but they may have significant side effects such as decreased bone mineral density, hot flashes, and mood or sleep disturbances. Due to these side effects, they should only be used for up to 1 year and with add back low dose estrogen and progesterone therapy. GnRH analogues are often used post-operatively to try to reduce endometriosis recurrence after surgery and the optimal duration is for 6 months. Research studies must be interpreted with caution as some do not have a control group for comparison, or the control group are women without treatment.

Methods: An electronic search of the PubMed database was performed using the MeSH terms such as, "endometriosis/surgery," and "gonadotropin-releasing hormone/agonists," to obtain articles published from 1988 until March 2020. Only English-language articles were included. Articles addressing the use of GnRH analogues in the peri-operative period for patients with endometriosis were included.

Key Content and Findings: Patients with deep infiltrating endometriosis (DIE) reporting deep dyspareunia may have significant improvement in sexual satisfaction and reduced pain after laparoscopic surgery for endometriosis followed by treatment with a GnRH agonist. After surgical removal of an endometrioma, suppressing ovulation can reduce endometrioma recurrence, but oral contraceptive pills or dienogest may be preferable over GnRH agonists due to improved side effect profiles. GnRH antagonists are a promising treatment for endometriosis pain in general, but there is little data available on using GnRH antagonists in the post-operative setting to reduce endometriosis recurrence.

Conclusions: The European Society of Human Reproduction and Embryology (ESHRE) recommends using a levonorgestrel intrauterine system or a combined oral contraceptive for 18–24 months post-operatively to reduce dysmenorrhea pain in patients with endometriosis. Individualized patient counseling on risks and benefits as well as individual patient factors should be used to help select whether GnRH agonists are used post-operatively to prevent endometriosis recurrence.

Keywords: Endometriosis recurrence; endometriosis surgery; gonadotropin-releasing hormone analogues (GnRH analogues)

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Introduction

Traditionally, laparoscopy is performed to obtain a definitive diagnosis of endometriosis based on pathology seen and obtained at the time of surgery (1). However, patients with suspected early stage endometriosis are often first treated with medical management, including oral contraceptive pills and nonsteroidal anti-inflammatory medications (1). Gonadotropin-releasing hormone (GnRH) analogues are a second line therapy, typically reserved for endometriosis pain that is resistant to first line medications. There are a wide range of first line medications to treat pain from endometriosis, including combined oral contraceptive pills or progestins (1,2). There are multiple progestin formulations that are effective for treating endometriosis pain, such as oral norethindrone acetate, injectable depot medroxyprogesterone acetate, or intrauterine levonorgestrel. When these medications fail to improve symptoms, available second line agents include aromatase inhibitors and GnRH analogues. GnRH analogue can refer to either agonist or antagonist medications.

GnRH agonists work by down-regulating the hypothalamic-pituitary-gonadal axis, ultimately leading to suppression of ovulation and reduced estrogen levels, a key hormone known to stimulate endometriosis (2,3). There are many GnRH agonists available that can be delivered through injection or by nasal inhalation, but these medications must be used carefully due to hypo-estrogenic side effects (2). The risks and benefits of GnRH agonists must be carefully weighed and discussed with each patient prior to use (4). Due to these side effects such as decreased bone mineral density, hot flashes, and mood or sleep disturbances, they should only be used for up to 1 year and with add back low dose estrogen and progesterone therapy recommended to mitigate these side effects (2,5).

GnRH antagonists work by competitively binding to and therefore inhibiting the GnRH receptor from forming a functional unit (2). Similar to GnRH agonists, this results in down-regulation of the hypothalamic-pituitary-gonadal axis, creating similar downstream effects including a hypoestrogenic state. What is unique to GnRH antagonists however is that they can be used in different doses, and at low doses, allow for some estrogen production to continue thus mitigating the side effects (2). While these medications traditionally come as an injection, more recently an oral form, Elagolix, was approved for treatment of endometriosis by the FDA in 2018 (2).

Surgery plays a critical role in endometriosis that is resistant to medical management, in the presence of endometriomas or ovarian involvement, and in the presence of deep infiltrating endometriosis (DIE) (6). A common use of a GnRH agonist is post-operatively, after a patient has undergone surgical removal of endometriosis, to try to reduce recurrence (1). As many as 72% of patients who undergo surgery may have a symptomatic recurrence or even require repeat surgery in 7 years' time (6). Some patients may even require three or more additional surgeries within 4 years of their initial endometriosis surgery (7). The goal of giving a GnRH agonist post-operatively is to eliminate small lesions that may not be seen or excised during surgery, while also preventing the formation of new lesions (7). While Guo proposes focusing on pre-operative and peri-operative interventions to reduce endometriosis recurrence, such as using beta-blockers and COX-2 inhibitors (6) here we will focus on the latest research concerning the use of GnRH analogues post-operatively to prevent endometriosis recurrence.

Methods

An electronic search of the PubMed database was performed using the MeSH terms, "endometriosis/drug therapy", "endometriosis/surgery", "gonadotropin-releasing hormone/agonists", "hormone antagonists/therapeutic use", and "post-operative care/methods" to obtain articles published from 1988 until March 2020. Only English-language articles were included. Two authors, EPN and EM screened titles and abstracts and only pertinent literature was included. Articles addressing the use of GnRH analogues in the peri-operative period for patients with endometriosis were included.

General effectiveness

GnRH analogues, including both agonists and antagonists, while effective in reducing endometriosis pain, are a second line therapy due to their side effects. While GnRH agonists have been clinically shown to suppress recurrent endometriosis, one histologic study found little if any effect of hormonal treatment, including a GnRH agonist, on the cellular morphologic changes in endometriosis growth (8). Women in this historic study underwent laparoscopic surgery for confirmation of endometriosis followed by hormonal treatment for 6 months. After the 6 months, the women underwent repeat surgery obtaining tissue for histological evaluation. In those with and without hormonal

treatment, there was no histologic difference in endometrial cell mitotic activity or endometriosis growth suppression, when one might expect to see a regression of active endometriosis in those on hormonal treatment (8). While a unique study in its ability to assess pathology after hormonal treatment, perhaps 6 months was not long enough to see a significant effect. In addition, this study did not focus on patients' symptoms and quality of life, which are arguably more important factors a patient and her physician must consider when determining whether treatment is a success or failure.

Dosing and duration of therapy

Duration of treatment with GnRH agonists are limited to 6 months, unless low dose estrogen and progesterone therapy is given, in which case they can be used for up to 1 year (2,5). This limitation exists to minimize harmful side effects such as decreased bone mineral density. If GnRH is to be used post-operatively, it is more effective to treat for 6 months than for a shorter 3-month period based on results of a meta-analysis of seven clinical trials that were looking at either patient symptoms or disease recurrence (7). This meta-analysis compared 328 post-operative patients who received a GnRH agonist with 394 control patients who did not, pooled from seven different randomized controlled trials (7). There was a good distribution of patients who received 3 months of treatment (four studies) compared to 6 months of treatment (three studies). GnRH agonist treatment for 6 months post-operatively did decrease the risk of endometriosis recurrence, however when analyzing the 3-month treatment group alone, there was no significant effect (7). Measures of recurrence varied between the different studies but included both symptoms and disease recurrence, theorizing that only 3 months of treatment may not be enough to see a clinical response, and thus reinforcing the need for longer duration of therapy.

When using a GnRH agonist, a low dose can be effective and have fewer menopausal side effects for women. In women with either stage III (moderate) or IV (severe) endometriosis who underwent laparoscopic surgery, a lower post-op dose of 1.88 mg GnRH was more effective than the higher 3.75 mg dose while still relieving patient's pain (9). This interventional study of 50 women assigned half of the women to receive a high dose of 3.75 mg of a GnRH antagonist monthly for 6 months post-op, while the other half of the women received a tapering of this dose, starting with only two doses of the higher 3.75 mg, but then receiving the 3rd through 6th monthly injections at a lower 1.88 mg dose (9). A strength of this study is that many end points were measured. One of particular interest was the change in bone mineral density before and after GnRH treatment, as well as the development of bothersome perimenopausal symptoms. And while both doses of GnRH agonist showed improvement in dysmenorrhea, the patients on the lower dose did not lose as much bone mineral density (1.2% loss of bone mineral density *vs.* 5.6%) compared to the higher dose. In addition, the low dose group reported fewer perimenopausal symptoms at both 16 and 20 weeks after treatment (9).

GnRH agonists after surgery for DIE

Patients' reported pain and symptoms drive their treatment, as not all women with endometriosis report pain or warrant medical or surgical intervention. Therefore, it is important to focus on research that addresses these patient driven outcome measures. One observational study that subdivided women into those with and without DIE, found that the majority of patients' reporting deep dyspareunia with or without DIE had a significant improvement in sexual satisfaction and reduced pain after laparoscopic surgery for endometriosis followed by 6 months of treatment with a GnRH agonist (10). This observational study included 98 patients who were followed for up to 1 year after completing 6 months of a post-operative GnRH agonist. By comparing patient's results from a sexual function and satisfaction questionnaire at the time of surgery and 1 year after resuming menses post-GnRH agonist treatment, the authors were able to show significant improvement in patients' sexual satisfaction (10). An impressive 45.9% of patients reported they had no deep dyspareunia in the post-survey, and in the sub-group with surgically documented and removed DIE of the uterosacral ligament, 84.4% reported improvement in their deep dyspareunia (10). While this is an observational study without a control group, it is still clinically important because many patients with endometriosis, especially those with evidence of DIE of the uterosacral ligament, have dyspareunia or otherwise impaired sexual function, which significantly impacts their quality of life (10).

In addition, women with DIE are more likely to require surgery, and due to the invasive nature of the disease, the risk of post-operative complications is estimated to be as high as 14% (4). This makes it even more prudent to focus on treatments that can reduce patients' symptoms

or recurrence of disease in hopes to avoid future, high risk surgery.

GnRH agonists after surgery for endometriomas

One targeted area in the literature is hormonal treatment for patients after surgical removal of an endometrioma. The goal is to suppress ovulation and hopefully decrease the risk of developing a new or recurrent endometrioma (4,11). Post-op prevention of endometrioma recurrence starts in the operating room. If an endometrioma is 3 cm or greater in size, complete cystectomy should be performed to reduce recurrence. Complete cystectomy is superior to draining or burning the cyst (4). Cystectomy, also results in reduced pain post-operatively.

After surgical removal of an endometrioma, for patients not attempting pregnancy, treatment with combined oral contraceptive pills can reduce recurrence by suppressing ovulation (4). Whether GnRH agonists are beneficial after endometrioma surgery is less clear.

One retrospective study found that despite treatment with hormonal suppression for at least 12 months post-operatively after ovarian endometrioma removal, 26% of patients had a recurrent endometrioma (11). However, this study had many limitations. The authors did not distinguish how the ovarian cyst was removed (whether by cystectomy, drainage, or electrocautery), potentially clouding the results, as recurrence would be expected to be higher in those who did not have a complete cystectomy. The authors also did not specify the kind of hormonal treatment used (combined oral contraceptives, progesterone only, or GnRH agonists) or have a control group to compare to (11).

Using an oral progestin, dienogest, post-operatively is effective for suppression of recurrent endometriomas with a more favorable side effect profile than a GnRH agonist (12,13). While both dienogest and a GnRH agonist might be equivalent in terms of disease recurrence (14-17), side effect profiles differ. In a prospective study of 52 patients who had surgery for ovarian endometriomas, post-operatively patients received either 6 months of a GnRH agonist followed by combined oral contraceptive, or 24 months of dienogest alone without a GnRH agonist (14). While there was no difference in endometrioma recurrence or patients' reported pain between the two groups, there was a difference in bone mineral density. Although both groups of women had decreases in their bone mineral, for those on dienogest, this decrease was not as severe (–2.3% on dienogest *vs.* –3.5% after the GnRH agonist) (14). While this difference was not statistically significant, clinically it suggests that dienogest may be preferable to reduce unnecessary additional bone mineral density loss.

The use of GnRH agonists is controversial due to the significant side effects patients often experience. A case series of 28 patients after endometrioma removal who were treated with 6 months of GnRH agonist followed by placement of a levonorgestrel intrauterine device (IUD) concluded that this was an effective treatment for preventing endometrioma recurrence (18). What is not mentioned however is that there was no comparison group for these patients (all patients received treatment) questioning our ability to make any positive conclusions. In addition, 10% of patients were unable to tolerate the full 6 months of GnRH treatment, and 28% reported unwanted menopausal symptoms (18).

The role of GnRH antagonists in post-operative endometriosis treatment

GnRH antagonists have gained more attention in recent years with the approval of the oral GnRH antagonist, Elagolix, for treatment of endometriosis pain (2). This is a potentially promising therapy as demonstrated in two double-blind, randomized, controlled, clinical trials that showed improvement in endometriosis pain on both high and low doses of this medication (19). Although patients still experienced hypoestrogenic side effects, with variations in dosing available, one can potentially mitigate these side effects with more control than GnRH agonists. While a promising treatment for endometriosis pain in general, there is little to no data available on using GnRH antagonists in the post-operative setting to reduce endometriosis recurrence and further studies are needed.

Other hormonal suppression modalities compared to GnRH agonists

The European Society of Human Reproduction and Embryology (ESHRE) updated their management guidelines for women with endometriosis in 2014. They recommend starting hormonal medication post-operatively to reduce the long-term endometriosis recurrence risk in women not desiring immediate pregnancy (4). While certain patient factors may influence choice of treatment, ESHRE favors using a levonorgestrel intrauterine system or a combined oral contraceptive for between 18 and 24 months post-operatively to reduce dysmenorrhea pain

(4,20). Every patient is different however, and other patient factors however, such as presence of an endometrioma, may instead lead to selection of a different medication.

Conclusions

Endometriosis pain and disease recurrence have a significant impact on a patient's quality of life. It is critically important to offer patients the most beneficial treatments for reducing endometriosis recurrence, especially after undergoing surgery. GnRH agonists have shown promise if used for a 6-month period with add back therapy post-operatively, however their hypo-estrogenic side effects can be very bothersome to patients and some patients are not able to tolerate them. For this reason, GnRH agonists are considered second line therapy, and often patients and physicians first try other medications with fewer side effects. GnRH agonists should be considered as one therapeutic option among many other hormonal treatments such as combined oral contraceptive pills, dienogest, or a levonorgestrel IUD. However, an individualized decision must be made after a personalized discussion of risks and benefits with each patient, especially as many patients gladly accept the side effect profile in exchange for improvement in pain. In the future, more women may be choosing GnRH antagonists to manage their endometriosis symptoms and reduce disease recurrence as these medications can be titrated to reduce side effects, potentially changing the paradigm of endometriosis treatment with GnRH analogues.

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Footnote

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