Recurrent Endometriosis: Contemporary Challenges

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Background: The recurrence of endometriosis after fertility sparing surgery poses a challenge to clinicians. Presently, no treatment option is curative and available medication only changes the hormonal milieu to suppress or delay disease recurrence.
Objective: The aim of this review was to present current literature on recurrent endometriosis including dilemmas in definition, risk factors for recurrence and medical options for the prevention of recurrent endometriosis after surgery.
Methods: A review of literature was done using PubMed, EMBASE and HERDIN, with the following keywords: endometriosis, endometrioma, endometriosis-associated pelvic pain, recurrence of endometriosis. The authors identified reviews, trials and guidelines. The population was limited to reproductive-aged women suspected of having endometriosis.
Results and Discussion: The recurrence rate of endometriosis after conservative surgery ranges from 7.1-56%. The incidence varies according to the criteria used to define recurrence: relapse of pain, physical examination findings, presence of endometrioma on imaging studies, increase in serum CA-125, and intraoperative findings during repeat surgery. The risk factors for disease recurrence include: young age, high body mass index, large endometriomas at diagnosis, severe pre-operative pain, intraoperative findings of extensive adhesions, and positive surgical margins. The identification of patients at high risk for recurrence will enable clinicians to give appropriate post-surgical therapy to prevent recurrence. The choice of pharmacologic agent after conservative surgery includes: combined hormonal contraceptive pills, progestogens, and GnRH agonist. Although no major difference was seen in the effect of available drugs used to relieve endometriosis- associated pain and prevent disease recurrence, differences exist in safety, tolerability and costs.
Conclusion: There is an urgent need to standardize the definition of recurrent endometriosis. Patients should be counselled on the need for long term medical management to delay disease recurrence. A step-wise approach and algorithm in the medical management for the prevention of endometriosis recurrence are proposed.

Keywords: recurrent endometriosis, endometrioma, pelvic pain

Introduction

Endometriosis is a chronic inflammatory condition characterized by the growth of endometrial glands and stroma outside the uterine cavity. It results in inflammation that may cause distressing symptoms such as: dysmenorrhea, dyspareunia, infertility, and chronic pelvic pain. The prevalence of endometriosis in the general population of reproductive-aged women is said to be approximately 10%[1], with disease prevalence increasing to 30% in infertile women and 40-60% in women with dysmenorrhea.[2] Since endometriosis is primarily a disease of reproductive aged women, it is managed through conservative

medical therapy and fertility sparing surgery.[3] Surgical intervention as an adjunct to medical management has been associated with decreased pain and increased pregnancy rates.[4] However, like medical management, surgical intervention is not always successful and recurrence of disease is common.[5]

Failure of surgical management and subsequent disease recurrence may be attributed to the following observations: 1) optimal debulking cannot always be attained due to challenging lesion location or extensive infiltration; 2) incomplete surgery may cause misclassification of disease persistence as possible recurrence, 3) microscopic disease may be present and not recognized intraoperatively, and 4) residual disease provides a focus for future recurrence.[5–7]

Objectives

The aim of this review was to present current literature on recurrent endometriosis including dilemmas in definition, risk factors for recurrence and medical options for the prevention of recurrent endometriosis after surgery.

Methods

A review of literature was done using PubMed, EMBASE and HERDIN, with the following key words: endometriosis, endometrioma, endometriosis-associated pelvic pain, recurrence of endometriosis. The authors identified reviews, trials and guidelines. The population was limited to reproductive-aged women suspected of having endometriosis.

Results

Definition of Recurrent Endometriosis

There is a dilemma of non-uniformity of studies because there is no standardized definition for endometriosis recurrence. Different studies would define recurrence as: relapse of pain, clinical or instrument detection, rise in CA 125 levels, and evidence of recurrence found during repeat surgery.[8] Rates of recurrence of endometriosis based on definition are summarized below (Table 1).

Table 1. Summary of recurrence rates after first line surgery for endometriosis based on definition*

Definition	No of Studies	Recurrence Rate %	Follow up (months)
Recurrence of pain	12	9.6 - 56	12-72
Clinical findings	5	12.1 - 56	16-60
Anatomical relapse	14	7.1 - 34.2	12-72
Significant increase in CA 125	2	9 - 30.6	24-48
Second look surgery	3	12 - 37	18-36

* Based on data reported in Ceccaroni M, et al. (2019): Eur J Contraception & Reprod Health Care[8]

Risk Factors for Endometriosis Recurrence

The recurrence of endometriosis after conservative surgery presents challenges in management because repeated surgeries will compromise ovarian function[9] and thus, medical therapy has to be maximized before proceeding to more invasive procedures. In 2014, the American Society of Reproductive Medicine advocated the maximal use of medical therapy to avoid repeated surgeries.[10] The use of pharmacological therapy for prevention after conservative surgery is recommended for patients with high risk of recurrence.[11] It is important to determine the risk factors for recurrent endometriosis so that the post-operative management of high risk patients can be optimized.[12] Several studies have looked into this.

In a retrospective study that analyzed 358 women with endometriomas with a minimum follow-up of 5 years from laparoscopic endometrioma excision, severity of dysmenorrhea (RR: 1.711, 95% CI: 1.175–2.493, p = 0.005) and postoperative pregnancy (RR: 0.649, 95% CI: 0.460–0.914, p = 0.013) were independent risk factors for the recurrence of ovarian endometriomas. The severity of dysmenorrhea pre-operatively and post-operatively can indicate a more advanced stage of disease. Extensive adhesions and inflammation can complicate advanced stages and incomplete resection of endometriotic lesions frequently occurs. Post-operative pregnancy was shown to have a protective effect on endometrioma recurrence and may be due to the hypoestrogenic state of pregnancy and absence of ovulation during that period.[11]

In a 2016 study by Tobiume, et al.[6], 352 patients who underwent surgery and were diagnosed with

endometriosis based on histopathology were followed up for a minimum of 29 months. They investigated the factors associated with the recurrence of pain and endometrioma in order to identify the likelihood of recurrence in each patient. This study concluded that the risk factors for pain recurrence differ from the risk factors for recurrence of endometrioma. The significant risk factors for the recurrence of endometrioma after surgery include: maximum tumor diameter, r-ASRM score, presence of pre-operative pain, post-operative improvement of pain, operative time, and operative blood loss. On the other hand, the significant factors for recurrent pain include: presence of pre-operative pain and post-operative improvement of pain.

The r-ASRM score defines the severity of the disease intra-operatively and a greater score correlates to longer operative time and greater blood loss. More severe disease, characterized by a higher r-ASRM score, is a risk factor for endometrioma recurrence. This may be due to the presence of more advanced disease or secondary to incomplete resection of lesions secondary to the extensive adhesions and inflammation in the advanced stages of endometriosis.[6]

A recent study tried to characterize lesion subtypes in first and subsequent surgeries to examine the evolution and compare the time required for subsequent surgery based on the initial lesion subtype. All recurrences were visually or histologically confirmed by surgery after complete surgical excision of endometriotic lesions. Three distinct endometriotic lesions: superficial peritoneal endometriosis, endometrioma, and deep infiltrating endometriosis were identified. In this study, the medial time to first recurrence was 31 months and time to first recurrent endometriosis surgery is independent from the endometriosis subtype observed at the initial surgery. In the subsequent surgery, the endometriosis subtype observed is likely to be the same as that seen during the previous surgery. A high percentage of patients presented with more severe lesion subtypes in the subsequent surgery, particularly deep infiltrating endometriosis. This trend towards more severe endometriosis subtypes in these patients implies that disease progression may occur overtime irrespective of surgical removal.[13]

In a retrospective observational study of women who underwent unilateral salpingo-oophorectomy (USO) for unilateral ovarian endometrioma, the recurrence rates on the contralateral ovary were: 8% at 12 mo, 10.2% at 24 mo, 12.7% at 36 mo, and 24.7% at 60 months. The post-USO recurrence rate was increased significantly in cases with contralateral side adhesions. This can be explained by microscopic disease that extends to the contralateral side even after successful removal of the endometrioma.[7]

In the paper by Nirgianakis, et al.[13], the risk factors for endometrioma recurrence can be classified into patient-disease related and surgery associated variables. Patient-disease related variables include: positive family history, young age, prior ovarian stimulation, high body mass index, absence of pregnancy post surgery, large endometrioma at diagnosis, advanced stage of disease, severe pre-operative pain, and high serum CA-125. The surgery-associated variables are: intraoperative findings of extensive adhesion, need for radical surgery, and positive surgical margins.

The identification of patients at high risk for recurrence based on the presence of risk factors will enable clinicians to give appropriate post surgical therapy to prevent recurrence.

Medical Management After Conservative Surgery

The goals of therapy in endometriosis are: 1) reduce pain, 2) increase the pregnancy rate for women who desire to have children, and 3) delay recurrence for as long as possible.[14] After conservative surgery, medical treatment is given to delay recurrence especially if a patient is not desirous of immediate pregnancy.

Endometriosis is an estrogen dependent condition and medical therapy suppresses endogenous estrogen production. Hormonal treatment also suppresses ovulation which in turn induces amenorrhea and creates a hypoestrogenic environment that inhibits ectopic endometrial growth and prevents disease progression. Discontinuation of hormonal suppressive therapy is usually followed by recurrence due to the return of hormonal stimulation of the endometriotic implants.

Hormonal therapies after surgery for endometriosis can be prescribed in two situations: 1) Post- operative adjunctive hormonal therapy within 6 months after surgery; which is prescribed with the aim of improving the outcome of surgery for pain; and 2) Secondary

prevention, which is prevention of recurrence of disease in the long term and is given for more than 6 months after surgery.

A Cochrane review on pre and post-operative medical therapy for endometriosis surgery evaluated the evidence for post-operative hormonal suppression for endometriosis and noted no evidence of decreased disease recurrence. Despite the seeming lack of evidence, guidelines and expert opinion continue to recommend the use of post-operative suppression for secondary prevention. Given the chronic nature of the disease and high rates of post-operative recurrence, patients are in need of a safe long term maintenance option for endometriosis.[15]

The choice of medical management depended on: 1) patient's age, 2) pain symptoms, 3) extent of disease, 4) reproductive plans, 5) treatment risks and side effects, and 6) cost considerations.[15]

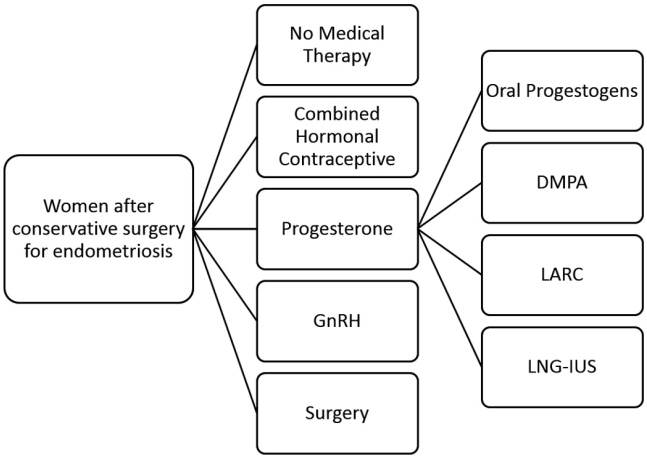

Figure 1. Management options of women after conservative surgery for endometriosis.

Medical treatment after conservative surgery for endometriosis can be in the form of combined hormonal contraceptive pill, progesterone, or GnRH agonist (Figure 1).

Combined Hormonal Contraceptives

In prescribing medications for endometriosis, the choice should be a balance of clinical efficacy with acceptable tolerability. It is important to achieve good compliance in order to avoid recurrence. A systematic review published in 2019 examined the efficacy of the use of hormonal contraception to improve the disease-related pain and disease recurrence. This review included 3 trials that looked into the recurrence of endometrioma after conservative surgery during treatment with combined hormonal contraceptives and 3 trials that looked into the recurrence of endometriosis associated pelvic pain after conservative surgery during treatment with combined hormonal contraceptives.[16] Oral contraceptives are considered to be a good option in terms of safety, tolerability and cost, and can also be administered for long periods of time.[17]

A study by Vercellini, et al.[18] compared always users vs ever users vs never users of a cyclic, low-dose, monophasic oral contraceptive pill containing ethinyl estradiol (0.02mg) and desogestrel (0.15mg). Recurrent endometriotic cysts were detected in 27% (74/227) of patients: 9% (9/102) in always users and 56% (26/46) in never users (P 0.001), with an adjusted OR 0.04 (95% CI 0.02-0.13). They concluded that the postoperative use of oral contraceptive pills prevents endometrioma recurrence (Table 2).

A retrospective cohort study reviewed the rate of ovarian endometrioma recurrence after laparoscopic surgery before and after the adoption of a "post-operative oral contraceptive recommendation" (EE/NETA) at the University of Tokyo Hospital. Always users were compared with patients who discontinued therapy and those who were not given hormonal therapy after surgery. Out of 87 patients, 23% had a recurrence. Among always users 2.9% (1/34) had a recurrence compared with 14.3% (2/14) in those who discontinued OC and 43.5% (17/39) in never users. With an RR 0.56 (95% CI 0.32-0.97), they concluded that the use of oral contraceptives after conservative surgery reduces the risk of endometrioma recurrence.[19]

In a randomized controlled trial, 217 patients who underwent conservative laparoscopic surgery for endometrioma were randomly allocated to three treatment arms: non-users group (no medical therapy prescribed after) and 2 groups who received ethinyl estradiol 0.02 mg/gestodene 0.075mg as cyclical hormonal therapy and continuous hormonal therapy. The crude recurrence rate within 24 months was 14.7% (11/75) in cyclic users, 8.2% (6/73) in continuous users, and 29% (20/69) in non-users. The mean diameter in the recurrent cysts was also significantly smaller in cyclic and continuous hormone therapy

Table 2. Summary of studies on recurrence of OMA after conservative surgery during treatment with CHC.

Study	Type of Study	No of Participants	Comparator	Duration	Recurrence Rate of OMA
Vercellini P, et al. 2008 (18)	Patient Preference Treatment	N=227	Always vs ever vs never users EE/DSG	28 mos	Total: 27% Always 9% (9/102) vs Never users 56% (26/46) adjOR 0.04 (95% CI 0.02-0.13)
Takamura M, et a.l 2009 (19)	Retrospective Cohort	N=87	Users vs discontinuous vs never-users EE/NETA	24 mos	Total: 23% Users 2.9% (1/34) vs Discontinuous14.3% (2/14) vs Never 43.5% (17/39) RR 0.56 (95% CI 0.32-0.97)
Seracchioli R, et al. 2010 (20)	RCT	N=217	CY vs CON vs NON EE/GSD	24 mos	Total: 17.1% Cyclic 14.7% (11/75) vs Continuous 8.2% (6/73) vs Non-users 29.0% (20/69) NS diff between cyclic and continuous

users. This study showed the efficacy of long-term, low-dose, monophasic OCP administration in the reduction of endometrioma recurrence after laparoscopic cystectomy.[20]

Several studies also looked into the effect of hormonal contraception on the recurrence of endometriosis-associated pelvic pain. A randomized controlled trial evaluated the efficacy of dienogest/estradiol valerate and GnRH-a in reducing the recurrence of pain in patients diagnosed with endometriosis thru laparoscopy. A visual analogue scale was used to rate the intensity of pain at 3, 6, and 9 months follow-up. No significant differences between the two groups were noted and both showed a marked improvement in the quality of life and satisfaction with both treatment arms. This study concluded that both dienogest/estradiol valerate and GnRH-a are equally efficacious in preventing endometriosis associated pelvic pain after laparoscopic surgery[17] (Table 3).

Morelli, et al.[21] conducted a randomized controlled trial to compare two commonly used postoperative medical therapy for prevention of endometriosis recurrence: dienogest/estradiol valerate and LNG-IUS. At 12 and 24 months, greater reduction in CA125 and VAS scores were noted for those taking oral contraceptives; the rate of recurrent endometrioma was lower in the oral contraceptive group, but the difference was non-significant.

Cyclic vs Continuous Regimen

Oral contraceptive pills can be taken cyclically or continuous. In the randomized controlled trial by Seracchioli, et al.[20], the use of both continuous and cyclic regimen significantly reduced the recurrence of endometrioma compared to non-users but there was no significant difference between cyclic users and continuous users in terms of recurrence. Another multi-center randomized controlled trial evaluated the effect of post-operative estroprogestin given for 6 months after surgery on the recurrence of endometrioma, recurrence of pain, and patient satisfaction at 3,6,12, and 24 months. Both regimens were equally effective insofar as postoperative pain and recurrence of endometrioma. However, the continuous regimen seems to be associated with significantly more adverse effects and discontinuation rates.[22]

In a prospective cohort study, 356 patients who underwent conservative surgery for endometriosis were given a 6 month course of cyclic OC or continuous OC. Both groups showed reduction in pain symptoms when compared to pre-operative scores. The continuous OC group showed a statistically significant reduction in recurrence rates for dysmenorrhea, endometrioma, and non-menstrual pelvic pain compared to the cyclic OC group.[23] In a meta-analysis that included the three previous studies

Table 3. Summary of studies on the recurrence of endometriosis associated pelvic pain after conservative surgery during treatment with combined hormonal contraceptives

Study	Type of Study	No of Participants	Comparator	Duration	Outcome
Granese R, et al. 2015 (17)	RCT	N=78	E2V+DNG vs GnRH-a	9 mos & 6 mos	Both therapies equally efficacious in preventing EAPP recurrence in the first 9 months of follow-up
Morelli M, et al. 2013 (21)	RCT	N=92	E2V+DNG vs LNG-IUD	24 mos	EP administration is significantly more effective than LNG-IUD in reducing pelvic pain and more effective in reducing recurrence rate but not at a significant level; LNG-IUD has significantly higher patient satisfaction
Seracchioli R, et al. 2010 (20)	RCT	N=311	CY vs CON vs NON EE/GSD	24 mos	Long-term postoperative use of OC pills can reduce the frequency and the severity of recurrent endometriosis-related dysmenorrhea
Muzzii L, et al. 2011 (22)	RCT	N=57	CY vs CON	12 mos	Both regimens were equally effective insofar as postoperative pain and recurrence of endometrioma CON regimen seems to be associated with significantly more adverse effects and discontinuation rates
Vlahos N, et al. 2013 (23)	Prospective cohort	N=365	CY vs CON EE/Drop	6 mos	Both cyclic and continuous OC improves pain symptoms when compared with preoperative scores Continuous OC appears to be associated with a reduced recurrence rate for dysmenorrhea, non-menstrual pelvic pain, and endometrioma but not for dyspareunia as compared with cyclic OC

mentioned, the authors concluded that a continuous oral contraceptive regimen may be suggested over a cyclic regimen because of a lower recurrence rate for dysmenorrhea (RR 0.24; 95% CI 0.06 to 0.91).[24]

Progestogens

It is the progestin component of oral contraceptive pills that induces decidualization and atrophy of eutopic endometrium, thus greatly reducing the amount of menstrual flow and retrograde menstruation.[17] Progesterone in the form of oral progestogens, depot medroxyprogesterone acetate, etonogestrel implant, and levenorgestrel intrauterine system are also given after conservative surgery for endometriosis.

In a systematic review and meta-analysis of endometriosis recurrence after treatment with dienogest post-operatively, the authors aimed to determine the rate of endometriosis recurrence defined as: 1) radiographic evidence of endometriosis (endometrioma on ultrasound or MRI, plaques, deep disease or other suggestive findings on MRI), 2) symptom recurrence in patients following conservative surgery treated with dienogest, and 3) findings from second look laparoscopy and to determine the odds of recurrence in women taking dienogest compared to controls who received no post operative hormonal suppression. It was shown that the incidence rate of endometriosis recurrence treated with dienogest was 2 per 100 women (95% CI: 1.43 to 3.11) compared with 29 per 100 women

who did not receive post operative treatment (95% CI: 25.66 to 31.74). They concluded that recurrence was significantly reduced with post operative dienogest compared with those managed expectantly.[25]

There is concern over bone mineral density changes with the prolonged use of dienogest; a decrease in BMD has been observed with treatment up to 52 weeks but partial recovery follows cessation of use. There is limited data with long term use of dienogest; however there are 2 studies ENVISIOeN (Effectiveness of dienogest in improving quality of life in Asian women with endometriosis) and VIPOS (Safety of Dienogest and other Hormonal Treatments for Endometriosis in Real World Clinical Practice) that are currently evaluating the safety and tolerability of dienogest use over extended periods of time. This will greatly help guide patient counselling and clinical decision making.

Another progestin commonly described is depot medroxyprogesterone acetate. A randomized controlled trial done in Thailand evaluated the efficacy and tolerability of DMPA versus continuous oral contraceptive pills in the treatment of endometriosis associated pelvic pain. Eighty-four patients, who underwent post conservative surgery for endometriosis were randomized to receive either intervention, at the end of 12 and 24 weeks. There was no difference in patient satisfaction between DMPA group and oral contraceptive group. The study concluded that both post-operative DMPA and continuous oral contraceptive pills are viable options for treatment after conservative surgery for endometriosis.[26]

A randomized controlled trial compared the efficacy of DMPA (150mg dose every 12 weeks) with the etonogestrel implant on patients with symptomatic endometriosis. Both treatments were shown to improve pain intensity during the follow-up period of 48 weeks and both had similar side effect profile and overall degree of satisfaction.[27]

The etonogestrel implant provides an alternative way of delivering progestogens. A subdermal application is able to achieve contraceptive action for at least 3 years, and as an effect has also been shown to decrease dysmenorrhea. Etonogestrel leads to an inactive or weakly proliferative eutopic endometrium. Etonogestrel can also affect the lesions directly through the progesterone receptors in the endometriotic lesions and indirectly by suppression of the HPO axis and thus reduced estrogenic stimulation of the lesions. A multicenter, prospective, observational study evaluated the effect of the ENG implant on pelvic pain, quality of life, and sexual function. They noted a decrease in dysmenorrhea and dyspareunia at 6 and 12months; however, there was no change in the mean diameters of the endometriomas.[28]

Another randomized controlled trial looked into the non-inferiority of etonogestrel implant compared to the levonorgestrel intrauterine device. One hundred three women with endometriosis associated pelvic pain were randomized to receive either etonogestrel implant or levonorgestrel IUS. Health-related quality of life improved significantly in all domains of the core and modular segments of the Endometriosis Health Profile-30 Questionnaire, with no difference between both treatment groups. Both contraceptives also significantly improved the mean visual analogue scale for endometriosis associated pelvic pain and dysmenorrhea. They concluded that both contraceptives improved pelvic pain, dysmenorrhea, and health related quality of life in endometriosis.[29]

The levonorgestrel intra-uterine system (LNG-IUS) is another progestogen widely studied in the medical treatment of endometriosis. It exerts its effects via several mechanisms: decidualizing the stroma, inducing glandular atrophy, and increasing apoptotic activity. LNG-IUS has an antiproliferative effect because it depletes the estrogen and progesterone receptors and inhibits estrogen induced growth factor.[30] In a Cochrane Review, they noted a significant reduction in the recurrence of painful periods in patients post surgery for symptomatic endometriosis managed with LNG-IUS compared with those managed expectantly (RR 0.22, 95% CI 0.08-0.60).[31]

In a pilot study on the effect of LNG-IUS in the management of endometriosis after conservative surgery, the absolute risk reduction of dysmenorrhea recurrence in patients given an LNG-IUS was 35% (95% CI, 9-61%). The insertion of the LNG-IUS postoperatively will prevent the recurrence of dysmenorrhea in one out of three patients within 1 year after surgery.[32]

In a randomized controlled trial comparing the effect of LNG-IUS vs depot GnRH agonist in women with chronic pelvic pain secondary to endometriosis, pelvic pain was decreased significantly from the first month throughout the six months of therapy in both groups with no significant differences between them.[33] A double-blind randomized controlled trial conducted

in 55 patients with endometriosis and moderate to severe dysmenorrhea post surgery evaluated the effect of LNG-IUS versus expectant management in the recurrence of endometriosis associated pelvic pain. At 12 months, the LNG-IUS groups had significantly lower pain scores for dysmenorrhea and non-cyclic pelvic pain compared with the control group. The number needed to prevent one case with dysmenorrhea within 1 year post surgery was three.[34]

While the previous studies looked at pain recurrence, a recent randomized controlled study evaluated the effect of the LNG-IUS on postoperative endometrioma recurrence. Eighty patients who underwent conservative surgery for symptomatic endometriosis were randomized allocated to a control group and LNG-IUS group. The main outcome was the recurrence of endometrioma 30 months post surgery; secondary outcomes included dysmenorrhea, non-cyclic pelvic pain, and CA125 levels. Those treated with LNG-IUS had significantly longer duration to dysmenorrhea recurrence, lower dysmenorrhea and pelvic pain scores, and lower serum CA125 levels; however, there was no difference in rates of endometrioma recurrence in both groups. The conclusion of this study was that while the LNG-IUS can prevent endometriosis associated pelvic pain, it is not effective for the prevention of endometrioma recurrence.[35]

Gonadotropin Releasing Hormone Agonists

Gonadotropin releasing hormone (GnRH) agonists are commonly used medical therapy after conservative surgery for endometriosis. GnRH analogues induce an estrogen deficient state, directly inhibit steroidogenesis, and suppresses the growth of endometrial implants.[17] A meta-analysis evaluated the effect on disease recurrence of GnRH agonist treatment. It included studies where GnRH agonist was given for 3 and 6 months and looked at effect of short-term (3 months) and long term (6 months) use of GnRH on endometriosis recurrence. Based on this meta-analysis, there was no significant difference of endometriosis recurrence rate between patients with 3 months post operative GnRH agonist treatment and the control group. On the other hand, the rate of endometriosis recurrence was significantly decreased in the group given 6 months GnRH agonist therapy vs the control group. The side effects of a hypoestrogenic state has limited the use of GnRH agonists to 6 months. This meta-analysis concluded that GnRH agonist should be given for 6 months in order to prevent recurrence.[36]

Future Therapies

Elagolix is an oral, non-peptide, gonadotropin-releasing hormone (GnRH) antagonist that has been showing promise in the treatment of endometriosis. In two double-blind, randomized, 6-month phase 3 trials, the effect of 150 mg once daily Elagolix and 200 mg twice daily dosing was compared with placebo in patients who were post surgery. Both doses were effective in improving dysmenorrhea and non-menstrual pelvic pain; but those in the treatment group also showed signs of hypoestrogenism: higher rates of hot flushes, higher levels of serum lipids, and greater decreases in bone mineral density from baseline.[37] Extension studies, which increased the treatment duration to 12 months, revealed sustained reductions in dysmenorrhea, non-menstrual pelvic pain, and dyspareunia. Hot flushes were the most commonly reported side effect.[38]

In the future, with more studies on the safety and tolerability of oral GnRH antagonists, Elagolix may play a bigger role in the medical management and prevention of recurrent endometriosis.

Longterm Management of Endometriosis

In the National Institute for Health and Care Excellence (NICE) guideline on the diagnosis and management of endometriosis, hormonal treatment after laparoscopic excision or ablation was recommended to be considered to prolong the benefits of surgery and manage symptoms.[39] The American Society of Reproductive Medicine guideline on endometriosis stated that ''Endometriosis should be viewed as a chronic disease that requires a lifelong management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures''.[40]

Based on the review of literature, the available medication alters the hormonal milieu and not the pathogenic mechanisms of endometriosis. The drugs in the market are suppressive; but there is no available drug for endometriosis which is curative. It should be emphasized that long term use of medications

is needed and once these drugs are discontinued, recurrence occurs. Based on several meta-analyses, no major differences exist in the effect of available hormonal drugs to relieve endometriosis-associated pelvic pain; however, differences exist in safety and tolerability profiles and cost of treatments.

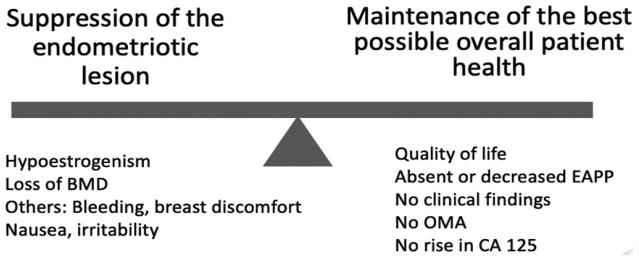

Figure 2. Striking a balance between suppression of lesions and overall patient health

The exposure of reproductive-age women to prolonged hypoestrogenism may cause unfavorable consequences; thus, the choice of medical management should attempt to strike a balance between the suppression of the endometriotic lesion and maintaining the best possible overall patient health (Figure 2).

Step-wise Approach for the Prevention of Recurrent Endometriosis

The authors would like to suggest a stepped-care approach for the prevention of recurrent endometriosis especially for women who do not want to attempt pregnancy immediately. This is an effort to limit the financial burden of medical treatment by using more affordable medications before proceeding to the more expensive ones (Figure 3).

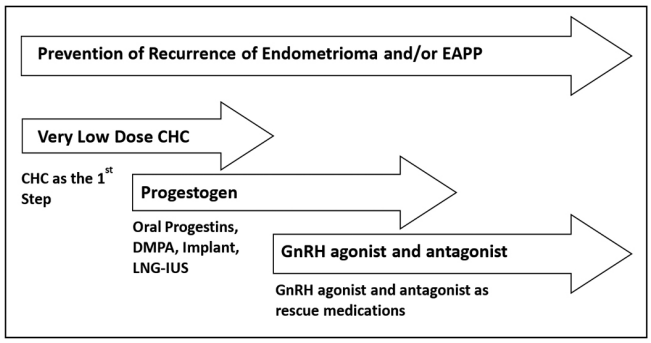

Figure 3. Proposed stepwise approach for the prevention of recurrent endometriosis after conservative surgery

Very low dose combined hormonal contraceptives should be considered the first line medication because they have been proven effective and are low cost. If pain recurs or continues to persist or the patient develops an endometrioma with the use of CHCs or if the patient cannot tolerate CHCs or it is contraindicated, a shift to progestogens may be done. DMPA, LARC and LNG-IUS have not been shown to be effective in decreasing endometrioma size. If the patient remains symptomatic with progestogens or the patient cannot tolerate it or it is contraindicated, then GnRH agonist and antagonist may be given as rescue medications (Figure 4). It is only after the failure of medical therapy that repeat surgery should be considered.

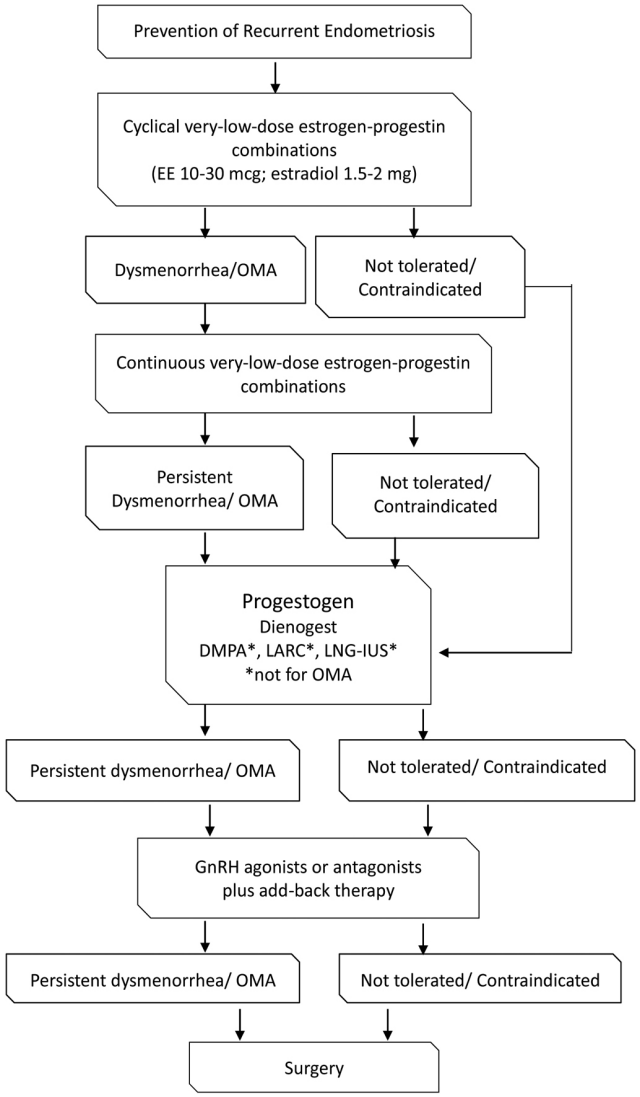

Figure 4. Proposed algorithm for the prevention of recurrent endometriosis after conservative surgery

Summary

In summary, we have reviewed and summarized current evidence on recurrent endometriosis. It is important to remember that available medication only changes the hormonal milieu and not the pathogenic mechanisms of endometriosis. At present, there is no available drug for endometriosis that is curative. Although no major difference was seen in the effect of available drugs used to relieve endometriosis-associated pain, differences exist in safety, tolerability and costs. Patients should be counselled on the need for long term management.

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