

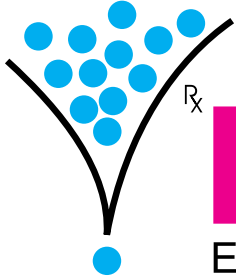


A FOGSI President's Initiative



KEY PRACTICE POINTS ON ENDOMETRIOSIS

In Management of Endometriosis, Adenomyosis & Chocolate Cyst



MiRumigest

Each tablet contains Dienogest 2mg

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**Highest Quality Raw Material
Imported From Europe**



- Safe and effective in reducing pain and size of Endometriotic lesion¹
- >80 months continuous safety studies²
- Prompt return to fertility³
- Anti-androgenic, No hypoestrogenic side effects⁴
- Effective in adolescent with suspected endometriosis⁵
- Lower recurrence rate post surgery⁶

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Dear FOGSIANS,

In this era of evidence-based medicine, Gynaecologists often must make decisions where neither evidence nor consensus exists. Fortunately, there is a growing body of evidence to assist in managing Endometriosis, Fibroids and OAB. With Key Practice Points, the idea is to regularly create evidence and consensus based practical approach to the diagnosis and management of indications, thereby ensuring a higher quality of care to patients.

Key Practice Points (KPP) from FOGSI supported in science through Science Integra will be an annual affair to bring the best talent across the country and get them to discuss, deliberate and create easy point of reference to practice better.

Hope you all will maximise from the KPP outputs and pass on further for the betterment of the community and the STREE in all. Our sincere gratitude to Alembic Pharmaceuticals for their educational grant for the Key Practice Points.

Best wishes!

Dr. Nandita Palshetkar

MD, FCPS, FICOG

President 2019 - Federation of Obstetrics & Gynecological Societies of India (FOGSI)

KEY PRACTICE POINTS ON ENDOMETRIOSIS

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- Panelists** : Dr. Rajendra Singh Pardeshi,
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From left to right: *Sitting* – Dr. Sheetal Sawankar, Dr. Rohan Palshetkar, Dr. Seema Pandey, Dr. Selvapriya Saravanan
Standing – Dr. Ameya Purandare, Dr. Meenu Agarwal, Dr. Priti Kumar, Dr. Asha Baxi, Dr. Parag Biniwale, Dr. Sudha Prasad, Dr. Pratik Tambe, Dr. Nandita Palshetkar, Dr. Hrishikesh Pai, Dr. Rajendra Singh Pardeshi, Dr. Ramani Devi, Dr. Oby Nagar

Introduction

Endometriosis, a complex disorder in women of reproductive age, is characterized by the presence of extrauterine endometrial tissue, pelvic pain, dysmenorrhea and infertility. Various reports have shown induced inflammation, neoangiogenesis, and proliferation of endometriotic implants due to an increase in some pro-inflammatory cytokines and growth factors in the peritoneal cavity of women with endometriosis.¹

The general incidence of endometriosis is estimated to be in around 10% of the women of reproductive age group. Worldwide, ≥176 million women are reported to suffer from endometriosis, and around 26 million in India are reported to have endometriosis. The incidence in infertile women ranges from 20% to 50%.^{2,3} Various studies conducted in Indian population have shown the incidence of endometriosis to range from 34% to 48% as diagnosed by laparoscopy.^{2,4}

Diagnosis of endometriosis

Endometriosis can be difficult to diagnose, with some studies showing a delay in diagnosis by 4–10 years, resulting in decreased quality of life and disease progression.⁵ Delay in diagnosis

may occur due to contraceptives causing hormonal suppression of symptoms, use of non-discriminatory examinations, misdiagnosis, and attitude towards menstruation and normalization of pain by the women, their mothers, family doctors, gynecologists or other “specialists”.⁶ Endometriosis cannot be ruled out by a normal examination and pelvic ultrasound.⁵

Clinical evidence

In a national case-control study, women with endometriosis had higher odds ratios [OR (95% CI)] for the following symptoms: abdominopelvic pain 5.2 (4.7–5.7), dysmenorrhea 8.1 (7.2–9.3), heavy menstrual bleeding 4.0 (3.5–4.5), infertility 8.2 (6.9–9.9), dyspareunia/postcoital bleeding 6.8 (5.7–8.2) and urinary tract symptoms 1.2 (1.0–1.3), compared with controls. In addition, risk factors for subsequent diagnosis of endometriosis included a history of diagnosis with ovarian cyst 7.3 (5.7–9.4), irritable bowel syndrome 1.6 (1.3–1.8), pelvic inflammatory disease 3.0 (2.5–3.6) and fibrocystic breast disease 1.4 (1.2–1.7). Increasing the number of symptoms increased the chance of having endometriosis.⁷

RECOMMENDATIONS

Signs and symptoms

Endometriosis can be suspected in women (including young women aged ≤17 years) presenting with one or more of the following (7 D's):⁵

- Dysmenorrhea
- Dyspareunia
- Dysuria
- Dyschezia
- Dysfunctional (abnormal) uterine bleeding
- Difficulty in conception
- Diffuse abdominal pain

RECOMMENDATIONS

Differential diagnosis of endometriosis

- Pelvic Inflammatory disease
- Irritable bowel syndrome
- Interstitial cystitis
- Pelvic adhesions
- Ovarian cysts (benign or malignant)
- Uterine malformation

The diagnosis of endometriosis should be considered in the presence of symptoms (7 D's). Clinicians should consider the differential diagnosis as well.

Physical/clinical examination

- An abdominal and pelvic examination should be conducted in women with suspected endometriosis to identify abdominal masses and pelvic signs, such as reduced organ mobility and enlargement, tender nodularity in the posterior vaginal fornix, and visible vaginal endometriotic lesions.⁵
- Clinical examination should be performed in all women suspected. In adolescents and/or women without previous sexual intercourse, wherein vaginal examination may be inappropriate, a rectal examination can be helpful for the diagnosis of endometriosis.⁸
- The diagnosis of deep endometriosis may be considered in women with (painful) induration and/or nodules of the rectovaginal wall found during clinical examination or visible vaginal nodules in the posterior vaginal fornix.⁸
- The diagnosis of ovarian endometrioma may be considered in women with detected adnexal masses.⁸

Medical technologies in the diagnosis

The diagnosis of endometriosis is first suspected based on the history and symptoms and signs, then verified by physical examination and imaging techniques and finally, a histological examination of specimens collected during laparoscopy proves it. The gold standard for the diagnosis of the disease is considered to be a combination of laparoscopy and the histological verification of endometrial glands and/or stroma. Technologies that can be used to prove or rule out the presence of endometriosis include laparoscopy, histology, ultrasound, MRI, and biomarkers.⁶

Ultrasound scanning⁶

- Transvaginal sonography (TVS) can be considered to diagnose rectal endometriosis in cases with suspected deep infiltrating endometriosis.
- TVS can be used in women with an adnexal mass with a suspicion of endometriosis to diagnose ovarian endometriosis.

Clinical evidence

A study was conducted to analyze the diagnostic value of TVS for non-invasive, presurgical detection of bowel endometriosis. Likelihood ratios (LRs) were recalculated in addition to traditional measures of effectiveness. The prevalence of bowel endometriosis varied from 24% to 73.3%. LR+ ranged from 4.8 to 48.56 and LR- ranged from 0.02 to 0.36, with wide confidence intervals. Pooled estimates of sensitivities and specificities were 91% and 98%; LR+ and LR- were 30.36 and 0.09; and positive and negative predictive values were 98 and 95%, respectively. Hence, TVS with or without the use of prior bowel preparation is an accurate test for non-invasive, presurgical detection of deep infiltrating endometriosis of the rectosigmoid.⁹

In women with symptoms suggestive of endometriosis and with normal ovarian size during TVS, the sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV), and diagnostic accuracy of TVS in diagnosing endometriosis were 85.3%, 80.7%, 84.1%, 82.1%, and 83.2%, respectively. A significant association was observed with TVS-based soft markers ($p < 0.05$) with endometriosis (ovaries not at the same level, high left ovary, ovarian fixation to uterus, tenderness on ultrasound, ovarian fixation to iliac vessels and non-visualization of left ovary) with sensitivities of 85.3%, 80.9%, 80.9%, 66.2%, 55.9%, and 55.9%, respectively. These markers

could be considered as positive soft markers to predict endometriosis. The addition of these soft markers could improve the sensitivity, specificity, PPV, NPV, and diagnostic accuracy to 97.3%, 98.5%, 95.7%, 89.9%, and 91.2%, respectively.¹⁰

RECOMMENDATIONS

- A thorough physical and clinical examination must be done to diagnose endometriosis
- Patients without previous sexual intercourse and/or adolescents, rectal examination can be helpful for diagnosis [ESHRE Guidelines]
- TVS can be used to diagnose ovarian endometrioma. Positive soft markers such as ovaries not at the usual position, kissing ovaries, ovarian fixation to uterus and iliac vessels and tenderness during ultrasound examination can be used to predict endometriosis
- TVS can be recommended to diagnose or rule out rectal/bladder endometriosis

Magnetic resonance imaging (MRI)

- Pelvic MRI can be considered to assess the extent of deep endometriosis involving the bowel, bladder, or ureter.⁵
- However, pelvic MRI should not be considered as the primary investigation to diagnose endometriosis in women with symptoms or signs suggestive of endometriosis.⁵
- MRI may not be useful to diagnose or exclude peritoneal endometriosis.⁶

Clinical evidence

A study conducted with MRI for detecting the presence of peritoneal endometriosis by

Stratton and co-workers in a case series of 44 women with a clinical suspicion of endometriosis showed that the prevalence of endometriosis was 86%; sensitivity was 69%, specificity was 75%, LR+ was 2.76, and LR- was 0.41. LRs were too low to justify the use of MRI to diagnose or exclude peritoneal disease. Overall, MRI had a diagnostic sensitivity of 38% and specificity of 74% compared with biopsy results for each lesion.¹¹

MRI can be considered as the modality of choice for preoperative diagnosis and planning of patient with deep infiltrating endometriosis (DIE). A study was conducted to determine the diagnostic accuracy of pelvic MRI, TVS, and transrectal sonography (TRS) in diagnosis of DIE which was conducted during a 2-year period including a total number of 317 patients with signs and symptoms of endometriosis. MRI had the highest accuracy (85.4%) when compared to TVS (75.7%) and TRS (67.8%) in different locations. However, specificity had a reverse trend, favouring MRI (93.9%, 92.8%, and 89.8% for TVS and TRS, respectively). MRI was also found to be superior to TRS and TVS in terms of sensitivity, specificity, and accuracy for retrocervical DIE lesions.¹²

RECOMMENDATIONS

- Pelvic MRI is not recommended as the primary investigation to diagnose endometriosis in women with symptoms or signs suggestive of endometriosis.
- MRI is recommended when USG examination is not suggestive or when there is deep infiltrating endometriosis, and patient requires extensive surgery or to rule out malignancy as it can characterize the lesion.

Biomarkers

- Serum CA-125 has been proposed as a candidate biomarker.⁶

Clinical evidence

A study was conducted to evaluate the clinical utility of serum CEA, CA-125, CA15-3, and CA19-9 levels in the diagnosis of endometriosis. Patients were divided into three groups: of 20 patients with stage I or II endometriosis; 18 patients with stage III or IV endometriosis and 20 patients who were the control group. All patients underwent a serum determination of CEA, CA-125, CA15-3 and CA19-9. CA-125 serum concentrations were significantly increased in patients with stage III or IV endometriosis ($p < 0.05$), while the levels of the other serum markers did not show any statistically significant difference. Therefore, there is an increase of CA-125 levels in patients with advanced endometriosis, compared with minor endometriosis and control women.¹³

CA-125 is considered as a valuable adjuvant in the follow-up of recurrence in patients with advanced endometriosis and initially elevated CA-125 levels. It is not an effective screening tool for patients with dysmenorrhea, or for monitoring therapy. A study was conducted to estimate the value of CA-125 for the diagnosis of endometriosis in women with dysmenorrhea, as well as its significance in monitoring therapy and follow-up. Elevated CA-125 (>35 U/ml) was reported in 86.70% of women with advanced

endometriosis, and in only 26.8% with minimal and mild endometriosis. It was also observed that one year after therapy, women with elevated CA-125 levels before treatment were without recurrence of endometriosis and with normal CA-125 levels.¹⁴

Laparoscopy

One school of thought suggests that medical management may be offered before performing an invasive procedure like a laparoscopy to obtain histological proof of the disease in women with symptoms and signs of endometriosis. Laparoscopy is not suggested if signs of deep endometriosis or ovarian endometriosis are not present on physical examination and imaging especially in adolescents and young adults.⁶

Clinical evidence

A study was conducted to test the efficacy of laparoscopy alone for diagnosing endometriosis. A total of 976 patients underwent laparoscopy and biopsy due to pelvic pain and/or infertility. In 468 (47.95%) of the cases, the clinical and laparoscopic findings were consistent with endometriosis, and this was confirmed histopathologically in 337 (34.5%). Among the remaining 508 patients, although the laparoscopy was performed for acute pelvic pain, eight were diagnosed with endometriosis from histopathological examination of the pelvic specimens obtained. Therefore, endometriosis was confirmed in 345 patients (35.3%). In comparison with the histopathology, laparoscopy alone presented 97.68% sensitivity, 79.23% specificity, 72% PPV and 98.42% NPV. Laparoscopy should be used in combination with histopathology for diagnosing endometriosis.¹⁵

In another study, a negative diagnostic laparoscopy (a laparoscopy during which no endometriosis is identified) seems to be highly accurate for excluding endometriosis and

RECOMMENDATIONS

- CA - 125 is not a specific biomarker for endometriosis
- It is not recommended for routine clinical use
- In some cases it may be of value for treatment follow up [Evidence Level A]^{3,6}

is therefore of use to the clinician in aiding decision-making. A positive laparoscopy (a laparoscopy during which endometriosis is identified) is considered to be less informative and of limited value when used in isolation without histology.¹⁶

A study was conducted to evaluate the PPV of laparoscopic diagnosis compared to biopsy findings by the severity of disease. The overall PPV was 87% for all patients. The PPV per biopsy of stage I-IV endometriosis was 66%, 78%, 92%, and 81% respectively. The PPV per patient of stage I-IV endometriosis was 75%, 89%, 100%, and 90% respectively. Stages II-IV were significantly more likely to be confirmed by biopsy than stage I disease. The PPV per patient was higher than the PPV per biopsy indicating that the ability to diagnose endometriosis may be improved by performing multiple biopsies. Therefore, in order to avoid misdiagnosis particularly in stage I disease, every attempt should be made to confirm the diagnosis by biopsy.¹⁷

RECOMMENDATIONS

- Laparoscopy should be used in combination with histopathology for diagnosing endometriosis
- Laparoscopy is recommended to diagnose endometriosis, although evidence is lacking that positive laparoscopy without histology proves the presence of the disease. However, a negative histology does not exclude it.
- It is recommended that clinicians should obtain tissue for histology in women undergoing surgery for ovarian endometrioma and/or DIE to exclude rare instances of malignancy

Medical management of endometriosis

Women with endometriosis are challenged with one or both of two major problems including endometriosis-associated pain and infertility. Endometriosis-associated pain includes dysmenorrhea, dyspareunia, dysuria, dyschezia, and non-menstrual pelvic pain. The treatments described can offer relief of pain symptoms, but symptoms often recur after discontinuation of therapy.

GDG recommends medical therapy for patients of endometriosis for³

1. Prevention of recurrence following surgery and for long term follow up
2. If recurrence occurs
3. In patients who refuse surgery (Evidence level GPP)

Clinicians should counsel women with symptoms presumed to be due to endometriosis [CPP, dysmenorrhea, and dyspareunia] thoroughly.

Treatment of endometriosis-associated pain

Empirical treatment of pain

Empirical analgesics and hormonal medication without a prior definitive laparoscopic diagnosis can be considered in women having pelvic pain with a high suspicion of endometriosis. This can avoid the invasiveness of the laparoscopic procedure, and also due to the ease of prescribing hormonal contraceptives, which is generally prescribed for the prevention of pregnancy. Other causes of pelvic pain should be ruled out before empirical therapy is started. If the patient does not react favorably to the prescribed medical or hormonal pain treatment, laparoscopy can be performed to exclude or diagnose endometriosis (and

possibly treat it at the same time). Presence or absence of endometriosis cannot be predicted with response to hormonal therapy.¹⁸

RECOMMENDATIONS

Counselling of women with symptoms suggestive of endometriosis is recommended, and treatment with adequate analgesia, combined hormonal contraceptives or progestogens is suggested.

Moreover, prescribing oral contraceptives in adolescents with pelvic pain without a definitive diagnosis of endometriosis may delay in diagnosing the disease. Further, prescribing oral contraception in young girls because of primary dysmenorrhea could indicate the diagnosis of deep endometriosis in later life.¹⁹

Hormonal therapies

Hormonal suppression can be a promising approach to treat endometriosis and its symptoms, which is a predominantly estrogen-dependent disease. Various factors should be considered when prescribing hormones to women suffering from endometriosis-associated pain.

- None of the hormones is free of side effects
- Treatments vary in severity and tolerability
- Significant cost differences between treatment groups
- Not all types of pain respond equally to hormonal treatment

Oral progestins

Oral progestins have been demonstrated to be effective in the treatment of endometriosis for a very long time. They were reported to reduce or eliminate pain symptoms in approximately 90% of the patients.²⁰

Dienogest for the treatment of endometriosis

Dienogest, a 19-nortestosterone derivative is another progestin that has been studied in the treatment of endometriosis. It is associated with high specificity for progesterone receptors. Decidualization and atrophy of the endometrial lesions have been reported with continuous administration of dienogest. It also has anti-inflammatory, anti-angiogenic, and anti-proliferative effects.²¹

Dienogest 2 mg once-daily administered in women with endometriosis for long-term (60-month) effectively reduced the endometriosis-associated pelvic pain (EAPP) and avoided pain recurrence post-surgery. Dienogest initiated after laparoscopy reduced the median EAPP score from 70 mm pre-surgery to 10, 10, 20, 20, and 20 mm, respectively, after 12, 24, 36, 48, and 60 months of treatment. Dienogest in women without surgery reduced the median EAPP score from 80 mm pretreatment to 20, 20, 30, 30, and 30 mm, respectively, after 12, 24, 36, 48, and 60 months of treatment. The spotting episodes and phases of depressed mood experienced by few women were clinically manageable.²²

Another study demonstrated that orally administered dienogest was effective in treating dysmenorrhea and pelvic pain associated with endometriosis. By the end of treatment, the total dysmenorrhea scores had significantly decreased ($p < 0.001$); mean ($\pm$ standard deviation) pain score for dysmenorrhea before and after treatment were 1.42 ± 1.1 and 0.1 ± 0.3 , respectively. A significant difference was also observed between the mean non-menstrual pelvic pain scores before and after treatment, 0.52 ± 0.6 and 0.18 ± 0.3 , respectively. Dienogest treatment also decreased the use of analgesics significantly by the end of the treatment ($p < 0.001$).²³

Another study showed that dienogest 2 mg/day was effective in reducing endometriotic lesions (11.4 ± 1.71 to 3.6 ± 0.95 , $p < 0.001$). The extended therapy with dienogest 2 mg/day also showed an improvement in pelvic pain after 24–52 weeks (-22.5 ± 32.1 and -28.4 ± 29.9 mm, respectively) with tolerable side effects. Dienogest can be considered as an alternative for controlling symptoms related to endometriosis.²⁴

A study by Muller et al demonstrated that pre-cycle medical intervention with dienogest was beneficial in women with ovarian forms of endometriosis undergoing IVF. Infertile women planning IVF after laparoscopic surgery of ovarian endometriomas were divided and treated with dienogest, a-GnRH and the 3rd group was not on any hormonal therapy within 6 months preceding IVF. The dose of gonadotropin per cycle was reported to be higher, while the number of retrieved oocytes was lower in non-hormonal group patients ($p < .001$). The cycle cancelation rate was 4.5 times higher than that those in the dienogest group and two times

higher than in patients with a-GnRH pre-cycle administration. Dienogest pre-treatment led to 2.5 times higher clinical pregnancy rate (44.7% versus 16.7%, $p = 0.012$) and three times higher delivery rate (36.8% versus 11.1%, $p = 0.013$) compared with the non-hormonal group.²⁵

Combined hormonal contraceptives

A systematic review of the evidence showed that combined hormonal contraceptives (CHC) were beneficial for the treatment of endometriosis-related pain. The CHC agents were reported to significantly reduce dysmenorrhea, pelvic pain, and dyspareunia from baseline in most studies; continuous administration seemed to be more useful than cyclic administration. The effectiveness of CHC agents for pain reduction was similar to or less than that of oral progestins and GnRH agonists.²⁶

Another study demonstrated that a 12-month treatment with a vaginal ring supplying 15 mcg of ethinyl estradiol and 120 mcg of etonogestrel per day or a transdermal system delivering 20 mcg of ethinyl E and 150 mcg norelgestromin per day was effective in reducing symptoms in women with recurrent moderate or severe pelvic pain after conservative surgery for symptomatic endometriosis. The ring was observed to be more effective than the patch in patients with rectovaginal lesions. According to an intention-to-treat analysis, 72% ring users and 48% patch users were satisfied with the treatment.²⁷

Use of combined low dose hormonal contraceptives reduces EAPP (Evidence level B).³

- Oral pills (Evidence level B)
- The use of vaginal contraceptive ring or a transdermal [estrogen/progestin] patch for EAPP has been recommended (Evidence level C)
- Continuous use of COC may be considered for EAPP (Evidence level C)

RECOMMENDATIONS

- Progestins must be considered as the first line of therapy considering the Evidence Level A.^{3,6}
- Use of progesterone [like MPA], oral or depot, norethisterone acetate, dienogest or danazol are indicated to reduce EAPP (Evidence Level A).
- Dienogest is recommended for the treatment of dysmenorrhea and pelvic pain associated with endometriosis, and is safe for long-term (up to 5 years) use in patients with or without surgery (Evidence Level A).
- Dienogest at the dose of 2mg/day is as effective as GnRH agonists but with significantly less side effects (Evidence Level A).

RECOMMENDATIONS

- Combined hormonal contraceptives can be considered to reduce EAPP. Continuous administration is suggested to be a preferred choice and more useful than cyclical administration.
- Use of a vaginal contraceptive ring or a transdermal (estrogen/progestin) patch to reduce EAPP may be considered.
- OCs can be considered in price conscious situation as second line treatment, taking into consideration the level of evidence (Evidence level B, C).

Danazol and cabergoline

Danazol improves the endometriosis associated painful symptoms by producing a high androgen/low estrogen environment (a pseudo menopause), which results in the atrophy of endometriotic implants. Treatment with danazol (including adjunctive surgical therapy) was effective in relieving painful symptoms related to endometriosis when compared to placebo. Laparoscopic scores were also improved with danazol treatment (including as adjunctive therapy) when compared with either placebo or no treatment. But the side effects were more commonly reported in those patients receiving danazol than for placebo.²⁸

A study showed that cabergoline 0.5 mg twice per week for 12 weeks demonstrated better results in decreasing the size of endometrioma, compared to LHRH-agonist (triptorelin acetate) by exerting antiangiogenic effects through vascular endothelial growth factor receptor-2 (VEGFR-2) inactivation. Around 64.7% of women treated with cabergoline had significant decrease in endometrioma size compared with 21.7% of the women treated with LHRH agonist.²⁹

RECOMMENDATIONS

- Oral danazol is effective in the treatment of EAPP but serious androgenic side effects limit its use. (Evidence level GPP).
- Cabergoline [0.5 mg weekly twice for 3 months] reduced EAPP in early lesions and reduces the size of endometrioma, with a comparable effect to GnRH agonist.

GnRH agonists

Interventional suppression of sex steroids can lead to atrophy of endometriosis lesions. Administration of gonadotropin-releasing hormone agonist (GnRHa) can be used to achieve this, which produces paradoxical suppression of follicle-stimulating hormone and luteinizing hormone release, and hence suppression of gonadal function. GnRHa usage markedly reduces normal ovarian production of estradiol (E2) and testosterone (T) and lowers the circulating levels of these hormones. Despite its benefits in reducing pelvic pain and other symptoms of endometriosis, GnRHa usage must be discontinued after a period of time, typically 12 months, because of concerns over loss of bone mineral density. Leuprolide, nafarelin, and goserelin are widely used in USA and others are available worldwide. The use of add-back sex steroids with GnRH analogues can help in preventing the negative effects of the GnRHa while maintaining an effective therapy for endometriosis.³⁰

A study showed that daily intranasal deslorelin with low dose estradiol ± testosterone ($E_2 \pm T$) add-back resulted in a significant reduction in severity of endometriosis symptoms and signs with few safety signals and minimal hypoestrogenic symptoms. Women with

pelvic pain and laparoscopically confirmed endometriosis were treated with a six-month course of daily intranasal deslorelin with concurrent administration of either transdermal E2, intranasal E2, or intranasal E2 + T. Efficacy data included evaluation of dyspareunia, dysmenorrhea, pelvic pain, tenderness, and induration.³⁰

Endometriosis symptoms and signs scores decreased in all treatment arms from a baseline average of 7.4 to 2.5 after 3 months of treatment and 3.4 after 6 months. BMD changes and incidence of hot flashes were minimal, and no endometrial hyperplasia was observed.³⁰

RECOMMENDATIONS

- GnRH agonists (nafarelin, leuprolide, deslorelin, goserelin or triptorelin), can be used as one of the options for reducing endometriosis-associated pain.
- Commonly used GnRH agonist are Leuprolide and Goserelin (Evidence level A).³
- A hormonal add-back therapy from the day of 1st dose to coincide with the start of GnRH agonist therapy is suggested. [OCP's/ Norethisterone 5mg daily with Calcium + Vit D3 Supplementation]
- GnRH agonists are recommended only for girls beyond 16 years due to adverse effects on BMD [Evidence Level A]⁶

Aromatase inhibitors

Estrogen stimulates expression of the COX-2 enzyme, thereby increasing the levels of prostaglandin E2 (PGE2), which is a potent stimulator of aromatase activity in endometriosis. This process leads to the continuous production of E2 and PGE2 in endometriotic tissue, wherein estrogens promote the growth and invasion

of endometriotic tissue and prostaglandins mediate pain, inflammation, and infertility. Hence, aromatase inhibitors (AIs) have been researched as a potential treatment option for women affected with endometriosis.³¹

A meta-analysis of 10 clinical studies that enrolled a total of 251 women showed that AIs decreased pain and improved quality of life when used in combination with gestagens or oral contraceptives in patients with endometriosis. Combination treatment with letrozole and norethisterone acetate was more effective than norethisterone acetate alone in reducing pain and dyspareunia.³² This combination was also associated with less severe side effects and fewer discontinuations than concomitant treatment with letrozole and a GnRH agonist, triptorelin.³³

Another meta-analysis of eight clinical studies demonstrated that AIs decreased pain, reduced the size of extrauterine endometrial lesions, and improved patients' quality of life when used in combination with gestagens, oral contraceptives, or GnRHa. One of the RCTs in this meta-analysis showed that the use of AIs for 6 months in combination with a GnRH (1.0 mg anastrozole+3.6 mg goserelin) was associated with a significant decrease in pain compared to aGnRH alone (3.6 mg goserelin) ($p<0.0001$), and significant improvement in patient-reported symptom severity (Multidimensional Patient Scores [$p<0.0001$]). Therefore, AIs are shown to have a promising effect on pain associated with endometriosis.³⁴

The ESHRE (European Society of Human Reproduction and Embryology) guidelines recommend concomitant use of AIs and oral contraceptives, progestogens, or GnRHa in patients with pain associated with drug-resistant and surgery-resistant recto-vaginal endometriosis.³⁵

RECOMMENDATIONS

- Aromatase inhibitors are the second line of therapy.
- They can be prescribed in combination with oral progestogens to reduce EAPP as well as to reduce the size of endometrial lesions.
- Als can also be prescribed in patients with pain associated with drug-resistant and surgery, resistant recto-vaginal endometriosis.
- Anastrozole [1 mg] and Letrozole [2.5 mg] can be given daily for 12 weeks with Progesterone add-back therapy (Evidence level B).³

Analgesics

Endometriosis is associated with elevated prostaglandin levels in peritoneal fluid and endometriotic tissue. Hence, non-steroidal anti-inflammatory drugs (NSAIDs) work by blocking the enzyme COX that is crucial for the production of the inflammatory mediators and can be effective for treating the endometriosis-associated pain.⁶

Clinical evidence

COX-2 specific inhibitors were observed to be effective and safe therapy in the management of pelvic pain associated with endometriosis. Both, pelvic pain and dyspareunia were improved. Rofecoxib had higher efficacy than placebo and no recurrence occurred, while in the placebo-treatment a 16% (2/12) occurred.³⁶

Various studies have also shown that the use of NSAIDs provided no evidence of a positive effect on pain relief in women with endometriosis. Moreover, no evidence showed

that any individual NSAID was more effective than another.³⁷

RECOMMENDATIONS

- NSAIDs or other analgesics to reduce endometriosis-associated pain should be considered (Evidence level GPP).
- Mefenamic acid is the commonly used NSAID when pregnancy is desired (Evidence level GPP).

Surgery

Although endometriosis can be managed medically in many cases, surgical management is an essential part of the treatment. In women with endometriosis-related pain, surgery is indicated in the following cases:

- Who cannot or do not wish to take medical therapies
- Acute surgical or pain events
- Deep endometriosis
- During concomitant management of other gynecologic disorders
- Patients seeking fertility with pain

In women with endometriosis-related subfertility, surgery may be indicated in:

- Women with hydrosalpinges undergoing IVF
- Management of ovarian endometriomas in specific circumstances
- When a patient requests surgery as an alternative to assisted reproductive technology (ART)

Ultimately, a combined approach of surgery followed by postoperative medical therapy is considered as the best long-term outcomes for recurrence of disease and symptoms.³⁸

Replacing diagnostic laparoscopy with 'See and treat approach'

Routine diagnostic laparoscopy may face the following challenges:

- The surgeon may fail to recognize lesions with an atypical appearance or the lesions may be very small and thus prevent pathologic specimen retrieval.
- Excision of peritoneal or deeper lesions at the time of diagnostic laparoscopy may not always be performed or possible.
- The surgeons' experience, the patient's history and comorbidities, and the extent of disease may determine the risk of complications.

Hence, to minimize exposure to multiple surgeries, surgery can be reserved for diagnostic confirmation and simultaneous treatment. Simultaneous confirmation of the pathology and treating the underlying condition can be done during single anaesthesia.³⁸

Clinical evidence

In a recent study, of the 1,315 patients diagnosed with endometriosis and operated with laparoscopy, 82.5% were in stage III and IV; 73.61% had endometrioma (regardless of having deep infiltrative endometriosis [DIE] or peritoneal involvement) and 26.39% had either DIE or peritoneal involvement without endometrioma. The pain VAS score which was 8.23 ± 2.03 prior to surgery decreased to 4.46 ± 2.47 in 93.07% of patients. Spontaneous pregnancy was achieved in 33.1% of infertile women and 25% became pregnant using intrauterine insemination (IUI) or assisted reproductive technique (ART) post-operatively.³⁹

Moderate quality evidence shows that laparoscopic surgery used to treat mild and moderate endometriosis reduces overall pain

and increases live birth or ongoing pregnancy rates. Compared with diagnostic laparoscopy, operative laparoscopic surgery was associated with decreased overall pain (measured as 'pain better or improved') both at six months (odds ratio (OR) 6.58, 95% CI 3.31 to 13.10, 3 RCTs, 171 participants, $I(2)=0\%$) and at 12 months (OR 10.00, 95% CI 3.21 to 31.17, 1 RCT, 69 participants). Compared with diagnostic laparoscopy, laparoscopic surgery was also associated with an increased live birth or ongoing pregnancy rate (OR 1.94, 95% CI 1.20 to 3.16, $p = 0.007$, 2 RCTs, 382 participants, $I(2) = 0\%$) and increased clinical pregnancy rate (OR 1.89, 95% CI 1.25 to 2.86, $p = 0.003$, 3 RCTs, 528 participants, $I(2) = 0\%$). When laparoscopic ablation was compared with diagnostic laparoscopy plus medical therapy (GnRHa plus add-back therapy), more women in the ablation group reported that they were pain-free at 12 months (OR 5.63, 95% CI 1.18 to 26.85, 1 RCT, 35 participants, low-quality evidence).⁴⁰

RECOMMENDATIONS

- Surgical treatment of endometriosis is effective for reducing endometriosis-associated pain
- Surgical laparoscopy in endometriosis can reduce the overall pain and also increase the live birth or ongoing pregnancy rate

Ablation versus excision of endometriosis

A systematic review and meta-analysis showed that the laparoscopy excision group had a significantly greater reduction in symptoms of dysmenorrhea (mean difference [MD] = 0.99; 95% confidence interval [CI], -0.02 to 2.00; $p=0.05$) and dyschezia (MD=1.31; 95% CI, 0.33-2.29; $p=0.009$) compared with ablation. One study demonstrated a significant reduction

in chronic pelvic pain (MD=2.57; 95% CI, 1.27-3.87; p=0.0001) and Endometriosis Health Profile-30 core pain scores (MD=13.20; 95% CI, 3.70-22.70; p=0.006) in the excision group as compared to ablation group. Hence, at 12 months after surgery, laparoscopic excision led to a significantly greater improvement in the symptoms of dysmenorrhea, dyschezia, and chronic pelvic pain secondary to endometriosis compared with ablation.⁴¹

RECOMMENDATIONS

- Excision of endometriosis implants can be considered over ablation for the management of endometriosis associated pain

Asymptomatic endometriosis

The incidental finding of peritoneal, ovarian or deep endometriosis without pelvic pain and/or infertility is termed as asymptomatic endometriosis. Around 3% and 45% of women undergoing laparoscopic sterilization have been observed to have asymptomatic peritoneal endometriosis.⁶

A study was conducted to evaluate if asymptomatic endometriosis diagnosed in connection with tubal sterilization is likely to cause symptoms later in the woman's life. Pelvic pain was more frequently reported by controls than by women with endometriosis (28% vs. 6%). There was no significant difference between the groups concerning dysmenorrhea, premenstrual pain, or dyspareunia, nor was there any significant difference in the hysterectomy rate. The risk that asymptomatic, minimal endometriosis found incidentally will become symptomatic is very low.⁴²

According to the Korean Society of Endometriosis, asymptomatic patients whose endometriosis

was incidentally discovered during operation do not need medical or surgical treatment.⁴³ Some researches had recommended excision of endometrioma, for a type of ovarian cancer may be related to endometriosis. However, the risk of ovarian cancer is very low and a definite relation has not been verified.⁴³

RECOMMENDATIONS

- The evidence shows that the risk of asymptomatic, minimal endometriosis found incidentally to become symptomatic is very low.
- Medical or surgical treatment is not required for asymptomatic patients whose endometriosis is incidentally discovered and should be followed up.

Recurrent endometriosis

Relapse of endometriosis symptoms is reported to occur in 40%–45% of women and 27% of women are readmitted for surgery within 5 years. Almost half of the women endometriosis require a second operation and just over a quarter will undergo three or more procedures. Therefore, an urgent need emerges to identify an effective means of reducing the risk of symptom recurrence.⁴⁴

Risk factors for recurrence

Bilateral pelvic involvement of endometriotic lesions, previous surgery, tenderness-nodularity at cul de sac, postoperative high revised American Fertility Society (rAFS) scores, younger age are all risk factors for the recurrence.⁴⁵

The causes for recurrence include:⁴⁶

- Deep endometriotic lesions: Deep endometriotic lesions located in the subperitoneal space may go completely unrecognized or be particularly difficult to visualize during laparoscopy or to access

during surgery. Additionally, lesions can be hidden by peritoneal adhesions of the pouch of Douglas.

- **Microscopic Foci:** Microscopic foci of disease (invisible at the time of surgery) could progress and under suitable conditions give rise to clinically significant disease.
- Development of endometriosis after hysterectomy in patients on with no previous history of endometriosis.
- Ovarian conservation with hysterectomy is associated with increased symptom recurrence and higher rates of re-operation. Ovarian preservation is of particular importance since many patients undergoing hysterectomy for endometriosis-associated pain are young women in whom an effort should be made to preserve at least one ovary. Ovarian conservation carried a 6.1-fold risk of recurrent pain and 8.1-fold risk of re-operation.
- **Ovarian Remnant Syndrome:** Recurrent endometriosis has been associated with the presence of residual ovarian tissue following oophorectomy. Dense pelvic adhesions, inflammatory conditions, such as endometriosis, peri-operative bleeding, and ovaries which are partially or wholly retroperitoneal, can all contribute to the unintentional preservation of ovarian fragments.

Management of recurrent endometriosis

Postoperative medical treatment can help in suppressing ovarian activity and can lead to atrophy of the lesions. Immediate application of medical treatment after desorption of all visible lesions and prescribing the treatment for a long enough period of time can prove to be effective.⁴⁵

Implementation of GnRHa therapy after bilateral laparoscopic ovarian endometrial cystectomy can improve the postoperative pregnancy rate, reduce ovarian recurrence, and has a lesser influence on ovarian reserve. In a recent prospective controlled trial, patients (n=62) undergoing laparoscopic bilateral endometrial cystectomies with GnRH agonist treatment group had superior cumulative spontaneous pregnancy rate (57.1% vs. 36.8%; $p<0.05$) and lower recurrence rate (12.7% vs. 27.4%; $p<0.05$).⁴⁷

Long-term cyclic and continuous postoperative use of OCP has shown to effectively reduce and delay endometrioma recurrence. The crude recurrence rate within 24 months was significantly lower in cyclic (14.7%) and continuous OCP users (8.2%) compared with nonusers (29%). The recurrence-free survival was significantly lower in nonusers compared with cyclic and continuous users. The mean recurrent endometrioma diameter at first observation was significantly lower in cyclic (2.17 ± 0.45 cm) and continuous users (1.71 ± 0.19 cm) compared with nonusers (2.73 ± 0.56 cm). The mean diameter increase every 6 months at followup was significantly reduced in cyclic users (0.31 ± 0.18 cm) and continuous users (0.25 ± 0.09 cm) versus nonusers (0.48 ± 0.3 cm).⁴⁸

In a recently conducted systematic review and meta-analysis, researchers demonstrated that a continuous oral contraceptive regimen, as opposed to a cyclic regimen, may be suggested after surgery for endometriomas because of lower dysmenorrhea recurrence rates. Lower recurrence rates for dysmenorrhea were obtained with a continuous schedule (RR, 0.24; 95% CI, 0.06-0.91; $p=0.04$). A continuous oral contraceptive schedule was associated with a nonsignificant reduction of cyst recurrence rates compared with a cyclic schedule (RR, 0.54; 95% CI, 0.28-1.05; $p=0.07$).⁴⁹

RECOMMENDATIONS

- Postoperative medical treatment for minimum of 6 months with either OCP, progestins or GnRH analogue is beneficial in reducing or delaying the recurrence of endometriosis (Evidence level A)
- Oral progestins (MPA, Dienogest, Danazol) are effective in reducing pain and preventing the growth of lesion after surgery (Evidence level A).³
- Dienogest has added advantage of being anti-inflammatory, anti-angiogenic, and anti-proliferative with less side effects.³
- LNG-IUS reduces EAPP as second line therapy (Evidence Level A-B). It also helps in regressing adenomyosis (Evidence Level B).⁶
- Recurrence of pain is managed with medical suppression - NSAIDs, progestins (Evidence level A), GnRH analogues (Evidence level A), combined hormonal therapy (Evidence level B), AIs.

Prevention of adhesions in endometriosis

Adhesion prevention whether de novo or by re-formation is one of the most important and neglected aspects of the treatment of endometriosis. Adhesions may lead to dyspareunia, chronic pelvic pain, infertility, intestinal obstruction, and complications at subsequent surgery. They may also deal with the development of some forms of the disease such as ovarian endometriomas and deep invasive nodules which may impede normal tubal performance, and impair follicular growth, pick-up of the oocyte after ovulation, and spermatozoa or embryo transport.⁵⁰

Management of adhesions

Strategies aimed at preventing adhesions formation after surgery can be divided into those associated directly with the surgical procedure and those involving the use of specific therapies, either pharmacologic interventions or the application of barrier agents.⁵⁰

Adhesiolysis is considered an important preliminary step in the surgical procedures for endometriosis because it can facilitate further operative steps such as endometrioma or deep nodules removal.⁵⁰

A study showed that oxidized regenerated cellulose absorbable barrier significantly reduces adhesion reformation after laparoscopic surgery for endometriosis. Twelve of 16 (75%) women treated with the oxidized regenerated cellulose barrier were free of adhesions, compared with two of 16 (12.5%) controls, a statistically significant difference ($p < 0.05$).⁵¹

Oxiplex/AP adhesion barrier gel was effective in reducing adhesions, compared to surgery alone. Patients with stage I-III endometriosis were randomized to Oxiplex/AP gel treatment (treated group) of adnexa, or surgery alone (control group) after laparoscopic surgical treatment of endometriosis. Control patients with at least 50% red lesions had a greater increase in ipsilateral adnexal adhesion scores than patients with mostly black or white and/or clear lesions. Treated patients with red lesions had a greater decrease in adnexal adhesion scores than control patients.⁵²

RECOMMENDATIONS

- Adhesiolysis either with oxidized regenerated cellulose absorbable barrier or adhesion barrier gel could be considered in the surgical procedures for endometriosis for preventing adhesions and associated complications in endometriosis patients.

Adenomyosis

A report showed that Dienogest was tolerable for long-term use until menopause and can be an alternative treatment option in some patients, especially those with type 2 adenomyosis, to avoid hysterectomy. Both the pain-severity score and analgesics-usage score decreased after the start of treatment with dienogest. The mean $\pm$ standard deviation changes from baseline for the pain score were -3.4 ± 1.8 at 24 weeks and -3.8 ± 1.5 at 52 weeks, respectively.⁵³

RECOMMENDATIONS

- **Dienogest may be useful in the long-term treatment of symptomatic adenomyosis (Evidence level B).³**
- LNG-IUS helps in regressing adenomyosis (Evidence Level B).⁶
- GnRHa conservative adenomyoma surgery can be done prior to insertions of LNG IUS to reduce size of adenomyotic uterus and therefore reducing expulsion rate.

Scar endometriosis

- It is rare disease (Incidence: 0.03%–0.1%) and its incidence is increasing following surgeries like LSCS, amniocentesis, hysterotomy, and laparoscopy (Iatrogenic transplantation of endometrial implants to the wound edge).
- It has non-specific symptoms such as cyclical pain and swelling at the scar site.
- Clinicians are suggested to use USG with colour Doppler and CT scan as a mode of investigation. True cut biopsy can be a mode of diagnosis.
- D/D - Stitch granuloma, lipoma, desmoid tumour, abscess, cyst, keloid, primary and secondary malignant nodule and inguinal or incisional hernias.

- Management of scar endometriosis is wide excision of mass with or without mesh repair.
- Role of medical therapy is to reduce the symptoms but not the size of the lesion.
- Preventive measures to be taken during LSCS are excluding the decidua during closure of the uterus, using different mops and needles for different layers.
- Suspect malignancy in the event of recurrence, even though the incidence is less than 1%.

RECOMMENDATIONS

For umbilical and cerebral & scar endometriosis - isolated case reports are available where Dienogest has been used as an alternative to surgery with some efficacy. Not possible to make a clinical recommendation.

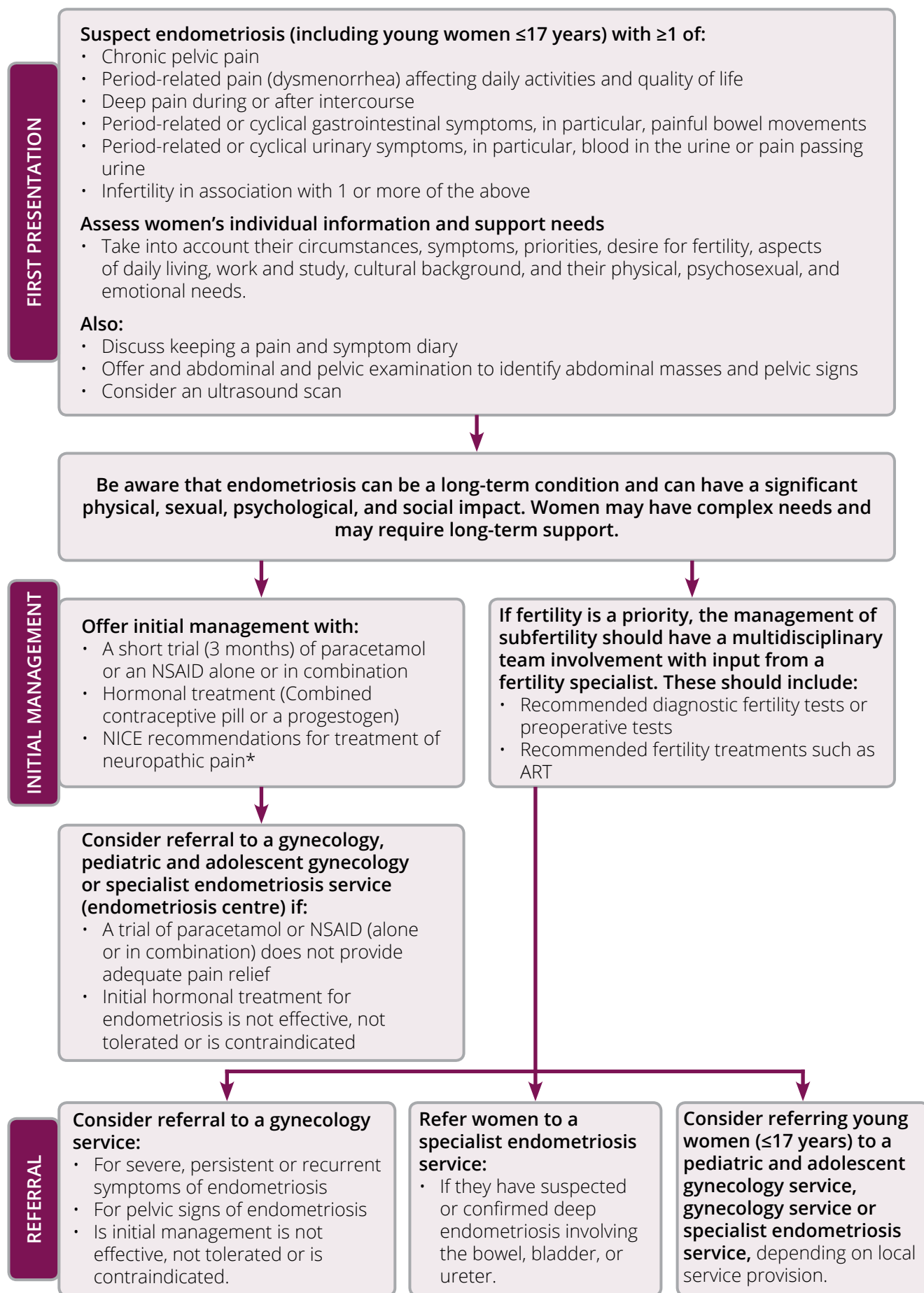
Interpretation of grading system of current Good Clinical Practice Recommendations (GCPR)

Grade	
A	Strongly recommended
B	Intermediate
C	Weak
D	Not evidence based
GPP	Expert/GDG consensus based

The evidence was further classified into four levels as mentioned in the Table below to facilitate the finding to be placed in the grades as mentioned above.

Evidence level	
1	Meta-analysis of randomized controlled trials, randomized controlled trials
2	Meta-analysis of nonrandomized prospective or case-controlled trials, nonrandomised controlled trial, prospective cohort study, retrospective case control study
3	Cross-sectional study, surveillance study (registries, surveys, epidemiologic study, retrospective chart review, mathematical modelling of database), consecutive case series, single case reports
4	No evidence (theory, opinion, consensus, review, or pre-clinical study)

Algorithm for the diagnosis and management of endometriosis⁵⁴



Do not use pelvic MRI or CA-125 to diagnose endometriosis

Consider transvaginal ultrasound:

- To investigate suspected endometriosis even if pelvic and/or abdominal examinations are normal
- For endometriomas and deep endometriosis involving the bowel, bladder or ureter

Consider a transabdominal ultrasound scan of the pelvis if a transvaginal scan is not appropriate

Do not exclude the possibility of endometriosis if the **abdominal** and/or **pelvic examinations or ultrasound or MRI are normal**.

Consider referral for assessment & investigation if clinical suspicion remains or symptoms persist.

Consider laparoscopy to diagnose endometriosis, even if the ultrasound was normal.

Discuss surgical management options with women with suspected/confirmed endometriosis:

- What laparoscopy involves, and that it may include surgical treatment (with prior patient consent)
- How laparoscopic surgery could affect endometriosis symptoms
- The possible benefits and risks of laparoscopic surgery
- The possible need for further surgery, including the possible need for further planned surgery for deep endometriosis involving the bowel, bladder or ureter.

During diagnostic laparoscopy, a gynecologist with training and skills in laparoscopic surgery for endometriosis should perform a systematic inspection of the pelvis.

If a **full systematic laparoscopy** is performed and is normal, explain to the woman that she does not have endometriosis and **offer alternative management**.

If fertility is a priority

Offer excision or ablation plus adhesiolysis to women with endometriosis not involving bowel, bladder or ureter.

Offer laparoscopic ovarian cystectomy to women with endometriomas.

Discuss the benefits and risks of laparoscopic surgery for deep endometriosis involving the bowel, bladder or ureter. This may include:

- Effect on the chance of future pregnancy
- The possible impact on ovarian reserve
- The effect of complications on fertility
- Alternatives to surgery
- Other fertility factors

Do not offer hormonal treatment to women with endometriosis who want to conceive.

Consider outpatient follow-up for:

- Deep endometriosis involving the bowel, bladder or ureter, or
- 1 or more endometrioma larger than 3 cm.

If fertility is not currently a priority

During diagnostic laparoscopy consider laparoscopic treatment of (if present):

- Peritoneal endometriosis not involving the bowel, bladder or ureter.
- Uncomplicated ovarian endometriomas.

Consider excision rather than ablation to treat endometriomas.

For deep endometriosis involving the **bowel, bladder or ureter, consider:**

- Pelvic MRI before operative laparoscopy
- 3 month course of GnRHa before surgery

Consider hormonal treatment after laparoscopic excision or ablation.

If hysterectomy is indicated:

- Excise all visible endometriotic lesions at the time of hysterectomy
- Discuss with the woman what a hysterectomy is, its risks & benefits, related treatments and likely outcome.

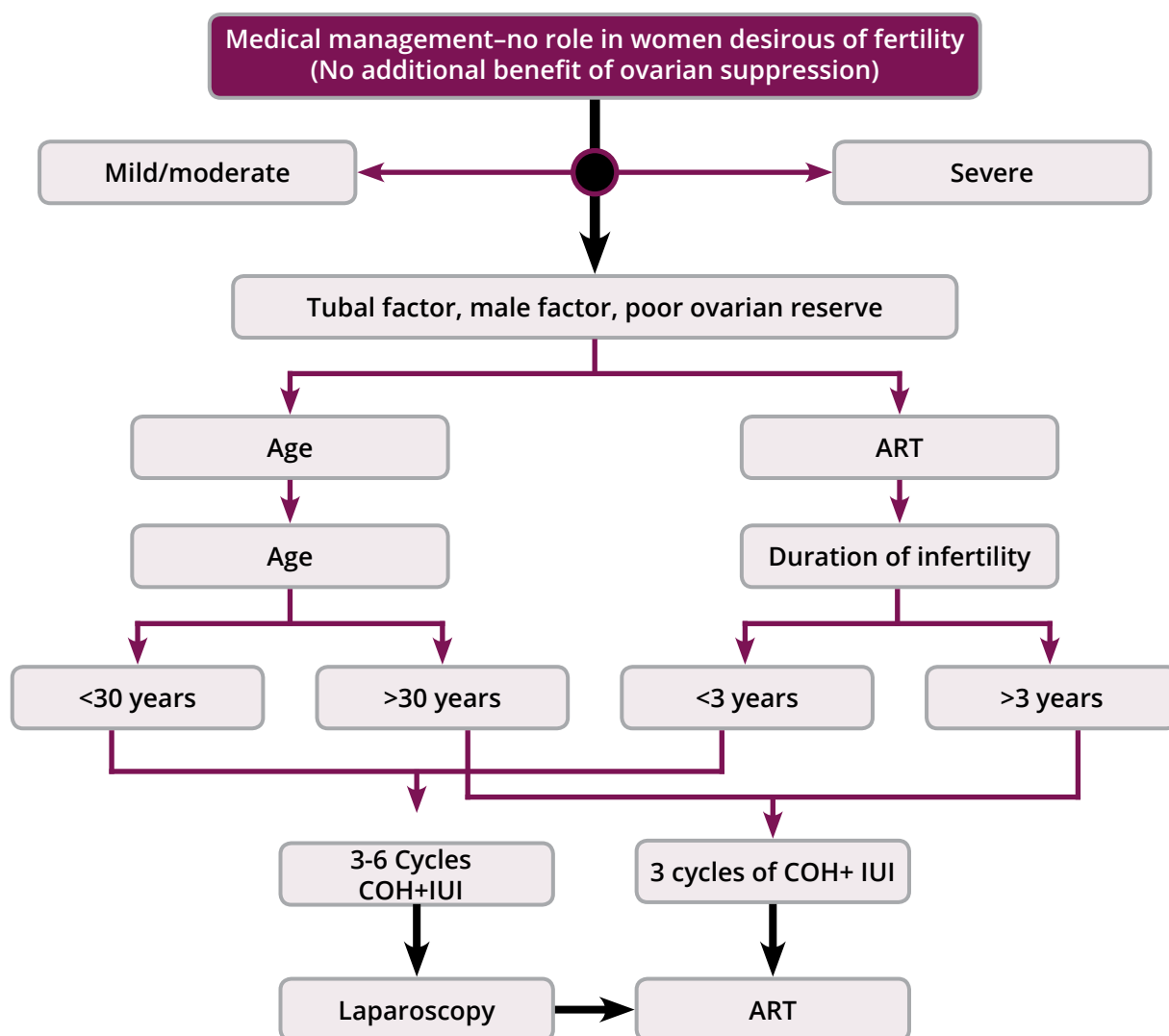
*NICE recommendations for treatment of neuropathic pain.

ART: Assisted reproductive technology; GnRHa: Gonadotropin-releasing hormone agonist; MRI: Magnetic resonance imaging; NSAID: Nonsteroidal anti-inflammatory drugs.

Pharmacological treatment for all neuropathic pain except trigeminal neuralgia⁵⁵

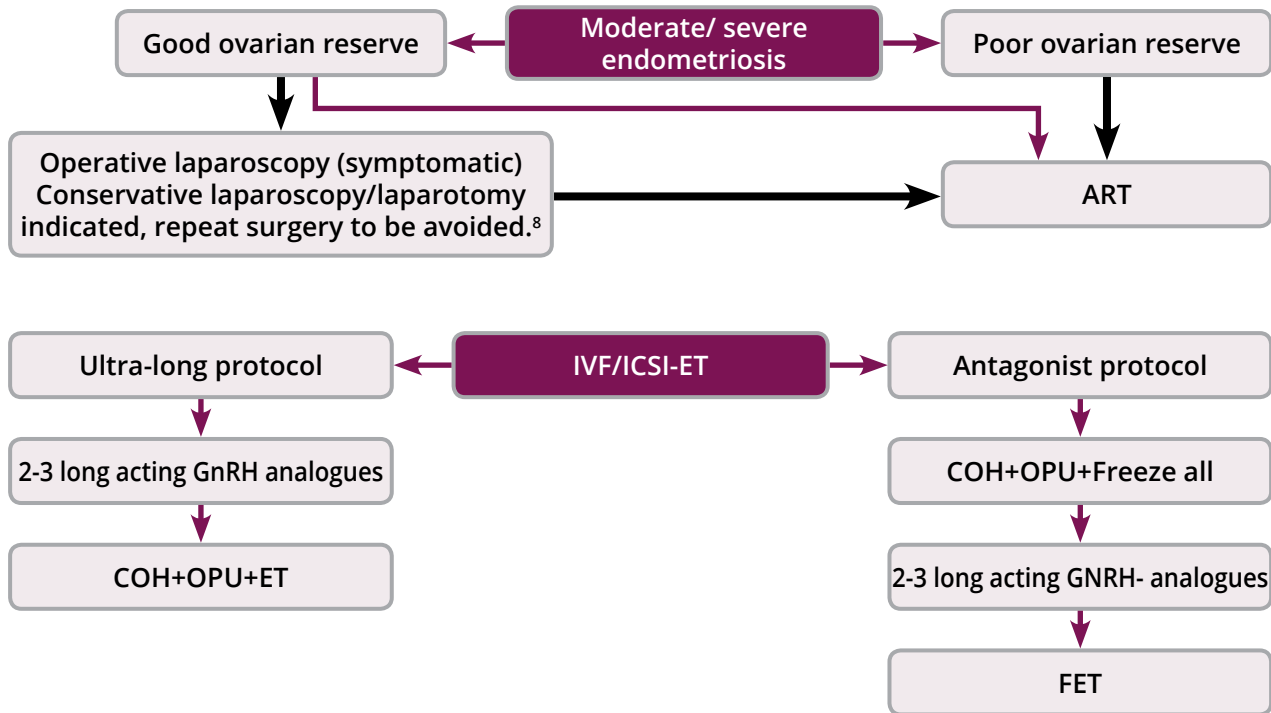
- Consider tramadol only if acute rescue therapy is needed.
- Offer a choice of amitriptyline, duloxetine, gabapentin, or pregabalin as initial treatment for neuropathic pain (except trigeminal neuralgia).¹
- If the initial treatment is not effective or is not tolerated, offer one of the remaining three drugs, and consider switching again if the second and third drugs tried are also not effective or not tolerated.

Infertility and endometriosis algorithm

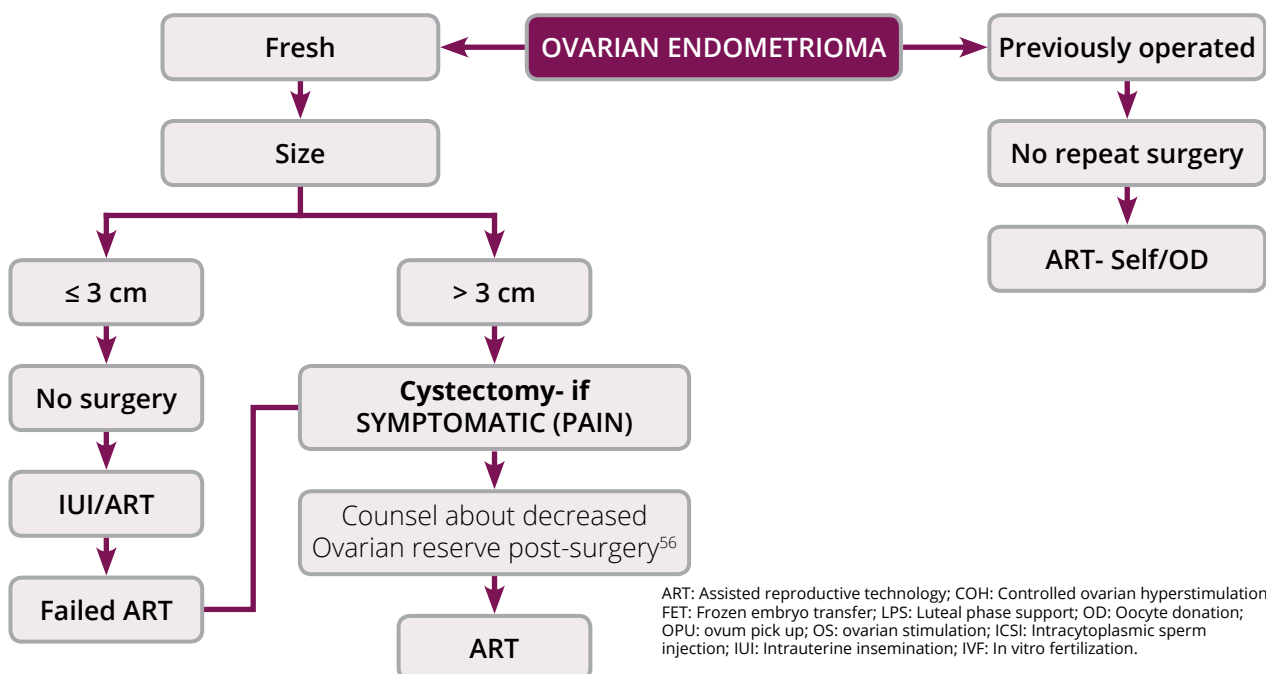


ART: Assisted reproductive technology; COH: Controlled ovarian hyperstimulation; IUI: Intrauterine insemination.

Insufficient data to recommend DL+DH before OS+IUI (not cost effective). Indications for DL+DH before IUI: symptomatic young patient, short duration of infertility, normal male factor, no ovulatory disorder, limited prior treatment.



LPS-with high dose of progesterone (dydrogesterone 30-60 mg for 12 weeks) relieves pain as well, or micronized progesterone (600-800 mg) more convenient, along with other modalities.



SUMMARY OF RECOMMENDATIONS

Endometriosis can be suspected in women (including young women aged ≤ 17 years) presenting with one or more of the following (7 D's):⁵

- Dysmenorrhea
- Dyspareunia
- Dysuria
- Dyschezia
- Dysfunctional (abnormal) uterine bleeding
- Difficulty in conception
- Diffuse abdominal pain

Differential diagnosis of endometriosis

- Pelvic inflammatory disease
- Irritable bowel syndrome
- Interstitial cystitis
- Pelvic adhesions
- Ovarian cysts (benign or malignant)
- Uterine malformation

The diagnosis of endometriosis should be considered in the presence of symptoms (7 D's). Clinicians should consider the differential diagnosis as well.

- A thorough physical and clinical examination must be done to diagnose endometriosis
- Patients without previous sexual intercourse and/or adolescents, rectal examination can be helpful for diagnosis [ESHRE Guidelines]
- TVS can be used to diagnose ovarian endometrioma. Positive soft markers such as ovaries not at the usual position, kissing ovaries, ovarian fixation to uterus and iliac vessels and tenderness during

ultrasound examination can be used to predict endometriosis.

- A TVS can be recommended to diagnose or rule out rectal/bladder endometriosis.
- Pelvic MRI is not recommended as the primary investigation to diagnose endometriosis in women with symptoms or signs suggestive of endometriosis.
- MRI is recommended when USG examination is not unequivocal or when there is deep infiltrating endometriosis, and patient requires extensive surgery or to rule out malignancy as it can characterize the lesion.
- CA-125 is not a specific biomarker for endometriosis.
- It is not recommended for routine clinical use.
- In some cases it may be of value for treatment follow up [Evidence Level A].^{3,6}
- Laparoscopy should be used in combination with histopathology for diagnosing endometriosis.
- Laparoscopy is recommended to diagnose endometriosis, although evidence is lacking that positive laparoscopy without histology proves the presence of the disease. However a negative histology does not exclude it.
- It is recommended that clinicians should obtain tissue for histology in women undergoing surgery for ovarian endometrioma and/or DIE to exclude rare instances of malignancy.

SUMMARY OF RECOMMENDATIONS

- Counselling of women with symptoms suggestive of endometriosis is recommended, and treatment with adequate analgesia, combined hormonal contraceptives or progestogens is suggested.
- Progestins must be considered as the first line of therapy considering the Evidence Level A.^{3,6}
- Use of progesterone [like MPA], oral or depot, norethisterone acetate, dienogest or danazol are indicated to reduce EAPP (Evidence Level A).
- Dienogest is recommended for the treatment of dysmenorrhea and pelvic pain associated with endometriosis, and is safe for long-term (up to 5 years) use in patients with or without surgery (Evidence Level A).
- Dienogest at the dose of 2 mg/day is as effective as GnRH agonists but with significantly less side effects (Evidence Level A).
- Combined hormonal contraceptives can be considered to reduce EAPP. Continuous administration is suggested to be a preferred choice and more useful than cyclical administration.
- Use of a vaginal contraceptive ring or a transdermal (estrogen/progestin) patch to reduce EAPP may be considered.
- OCs can be considered in price conscious situation as second line treatment, taking into consideration the level of evidence (Evidence level B, C).
- Oral danazol is effective in the treatment of EAPP but serious androgenic side effects limit its use. (Evidence level GPP).
- Cabergoline [0.5 mg weekly twice for 3 months] reduced EAPP in early lesions and reduces the size of endometrioma, with a comparable effect to GnRHa.
- GnRHa (nafarelin, leuprolide, deslorelin, goserelin or triptorelin), can be used as one of the options for reducing endometriosis-associated pain.
- Commonly used GnRH agonist are Leuprolide and Goserelin (Evidence level A).³
- A hormonal add-back therapy from the day of 1st dose to coincide with the start of GnRHa therapy is suggested. [OCP's/ Norethisterone 5mg daily with Calcium + Vit D3 Supplementation]
- GnRHa are recommended only for girls beyond 16 years due to adverse effects on BMD [Evidence Level A]⁶
- Aromatase inhibitors are the second line of therapy.
- They can be prescribed in combination with oral progestogens to reduce EAPP as well as to reduce the size of endometrial lesions.
- Als can also be prescribed in patients with pain associated with drug-resistant, surgery, resistant recto-vaginal endometriosis.
- Anastrozole [1 mg] and Letrozole [2.5 mg] can be given daily for 12 weeks with progesterone add-back therapy (Evidence level B).³
- NSAIDs or other analgesics to reduce endometriosis-associated pain should be considered (Evidence level GPP).

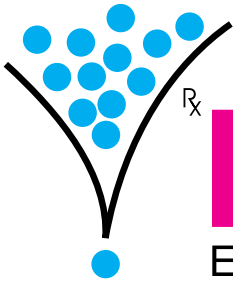
SUMMARY OF RECOMMENDATIONS

- Mefenamic acid is the commonly used NSAID when pregnancy is desired (Evidence level GPP).
- Surgical treatment of endometriosis is effective for reducing endometriosis-associated pain
- Surgical laparoscopy in endometriosis can reduce the overall pain and also increase the live birth or ongoing pregnancy rate
- Excision of endometriosis implants can be considered over ablation for the management of endometriosis associated pain.
- The evidence have shown that the risk of asymptomatic, minimal endometriosis found incidentally to become symptomatic is very low.
- Medical or surgical treatment is not required for asymptomatic patients whose endometriosis is incidentally discovered and should be followed up.
- Postoperative medical treatment for minimum of 6 months with either OCP, progestins or GnRH analogue is beneficial in reducing or delaying the recurrence of endometriosis (Evidence level A).
- Oral progestins (MPA, Dienogest, Danazol) are effective in reducing pain and preventing the growth of lesion after surgery (Evidence level A).³
- Dienogest has added advantage of being anti-inflammatory, anti-angiogenic, and anti-proliferative with less side effects.³
- LNG-IUS reduces EAPP as second line therapy (Evidence Level A-B). It also helps in regressing adenomyosis (Evidence Level B).⁶
- Recurrence of pain is managed with medical suppression - NSAIDs, progestins (Evidence level A), GnRH analogues (Evidence level A), combined hormonal therapy (Evidence level B), and AIs.
- Adhesiolysis either with oxidized regenerated cellulose absorbable barrier or adhesion barrier gel could be considered in the surgical procedures for endometriosis for preventing adhesions and associated complications in endometriosis patients.
- **Dienogest may be useful in long-term treatment of symptomatic adenomyosis (Evidence level B).**³
- LNG-IUS helps in regressing adenomyosis (Evidence Level B).⁶
- GnRH analogues/conservative adenomyoma surgery can be done prior to insertions of LNG IUS to reduce size of adenomyotic uterus and therefore reducing expulsion rate.
- For umbilical, cerebral, and scar endometriosis - isolated case reports where Dienogest has been used as alternative to surgery with some efficacy. Not possible to make a clinical recommendation.

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