ENDOMETRIOSIS

CHI Formulary Development Project

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM- September 2023

To the CHI Original Endometriosis Clinical Guidance- Issued May 2020

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Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

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Abbreviations

ACOG	American College of Obstetricians and Gynecologists
ART	Assisted Reproductive Technology
CHI	Council of Health Insurance
COC	Combined Oral Contraceptive
CPG	Clinical Practice Guideline
ESHRE	European Society of Human Reproduction and Embryology
FDA	U.S. Food and Drug Administration
GnRH	Gonadotropin-Releasing Hormone
GPP	Good Practice Point
IDF	CHI Drug Formulary
LEP	Low-Dose Estrogen–Progestin
LNG-IUS	Levonorgestrel-Releasing Intrauterine System
MRI	Magnetic Resonance Imaging
NICE	National Institute for Health and Care Excellence
NSAID	Non-Steroidal Anti-Inflammatory Drug
OC	Oral Contraceptive
SFDA	Saudi Food and Drug Authority
SOGC	Society of Obstetricians and Gynaecologists of Canada
US	Ultrasound

Executive Summary

Endometriosis is a disease that occurs in females of childbearing age. It is a disease that mainly affects the genital system and refers to the implantation or growth of endometrial-like tissue (glands and/or stroma) outside the uterine mucosa. It is usually difficult to diagnose and can sometimes go undiagnosed for years. In general, laparoscopy is the most common way to diagnose endometriosis. The main manifestations of this disease are chronic pelvic pain and pelvic cysts.

At a global level, the World Health Organization has estimated the incidence of endometriosis in 2023 at around 190 million, affecting as high as 10% of women of reproductive age worldwide[1]. In the Kingdom of Saudi Arabia, the prevalence is thought to be underestimated, but it is also assumed that at least 10% of all women of reproductive age are affected by the disease[2].

The direct medical cost range for endometriosis patients in 2022 exhibited considerable variability, spanning from US$1,459 to US$20,239 per year, with similar variations in indirect costs ranging from US$4,572 to US$14,079[3]. However, limited data are currently available regarding the disease's economic burden at the individual patient level[3].

CHI issued Endometriosis clinical guidelines after thorough review of renowned international and national clinical guidelines in May 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI Endometriosis clinical guidance and seeks to offer guidance for the effective management of Endometriosis. It provides an **update on the Endometriosis Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update were summarized, being **the issuance of updated versions of previously reviewed guidelines** namely The European Society of Human Reproduction and Embryology (ESHRE) guideline: management of women with Endometriosis (**2022**)[4] . Moreover, **new guidelines are added to the report** such as the Australian clinical practice guideline for the diagnosis and management of endometriosis (**2021**)[5], and the Clinical practice guidelines for Endometriosis in Japan (The 3rd edition) (**2022**)[6].

After carefully examining clinical guidelines and reviewing the SFDA drug list, there are no new drugs to be added to the CHI formulary, and there are no new drugs approved by the FDA. Three drugs are no longer SFDA registered, and it is advisable

to delist them from CHI formulary: Acemetacin, Estradiol Hemihydrate & Drospirenone, and Ethinylestradiol & Norgestimate.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in Endometriosis therapeutic management.

Below is a table summarizing the major changes based on the different Endometriosis guidelines used to issue this report:

Table 1. General Recommendations for the Management of Endometriosis

Management of Endometriosis		
General Recommendations	**Level of Evidence/ Grade of Recommendation**	**Reference**
Diagnosis of Endometriosis		
A normal abdominal or pelvic examination, ultrasound, CT, or MRI does not exclude the possibility of endometriosis. If clinical suspicion remains or symptoms persist, consider referral for further assessment and investigation	Evidence-based recommendation, very low quality of evidence	2021 Australian Guidelines[5]
Clinical examination: a clinical pelvic exam is an important part of an initial assessment to investigate suspected endometriosis- consider offering a pelvic exam, or an abdominal exam if not appropriate	Evidence-based recommendation, very low quality of evidence	2021 Australian Guidelines[5]
Consider laparoscopy to diagnose and treat people with suspected endometriosis, even if the ultrasound is normal	Evidence-based recommendation, very low quality of evidence	2021 Australian Guidelines[5]
For Treatment of Endometriosis-Associated Pain		
NSAIDs (alone or in combination with other agents) are recommended as first line.	Weak recommendation, Very low evidence	ESHRE Guideline: Management of Women with Endometriosis 2022[4]

Advise people that there is no evidence for or against the use of anti-neuropathic medications for pain associated with endometriosis	Consensus-based recommendation	2021 Australian Guidelines[5]
Chinese Herbal Medicine: Shakuyakukanzoto and tokishakuyakusan can be used for menstrual pain relief in unmarried and adolescent women.	No level of recommendation	2022 Japanese guidelines[6]
Hormone therapies such as OCs, LNG-IUS, GnRH agonists, and progestins are recommended	Strong recommendation, Moderate evidence	ESHRE Guideline: Management of Women with Endometriosis 2022[4]
	Level IB recommendation	2022 Japanese guidelines[6]
Hormone preparations after surgery should be prescribed to prevent progression and recurrence.	Level IIIC recommendation	2022 Japanese guidelines[6]
Combined hormonal contraceptives (oral, vaginal ring, or transdermal) can be considered to reduce dyspareunia, dysmenorrhea, and non-menstrual pain associated with endometriosis.	Strong Recommendation, Low evidence	ESHRE Guideline: Management of Women with Endometriosis 2022[4]
Progestogens can be considered.	Strong recommendation, Low evidence	ESHRE Guideline: Management of Women with Endometriosis 2022[4]
GnRH agonists can be prescribed, although evidence is limited regarding dosage or duration of treatment.	Strong recommendation, Low evidence	ESHRE Guideline: Management of Women with Endometriosis 2022[4]
GnRH antagonists can be considered, although evidence is limited regarding dosage or duration of treatment.	Weak Recommendation, Moderate	ESHRE Guideline: Management of Women with

	evidence	Endometriosis 2022[4]
Aromatase inhibitors are recommended for pain refractory to medical/surgical treatment and may be given in combination with other hormonal treatments.	Strong recommendation, Low evidence	ESHRE Guideline: Management of Women with Endometriosis 2022[4]
Surgical Therapy		
Hysterectomy is recommended for patient who have failed therapy and do not wish to conceive, although it will not necessarily cure the disease or its symptoms.	Weak recommendation, Low evidence	ESHRE Guideline: Management of Women with Endometriosis 2022[4]
Postoperative hormone therapy can be used to prevent recurrence of ovarian endometriotic cysts, and long-term administration of OCs/LEPs and dienogest may help prevent postoperative recurrence.	Level IA recommendation	2022 Japanese guidelines[6]
If surgery is performed for endometriosis, it should be performed by laparoscopy rather than laparotomy, unless there are contraindications	Evidence-based recommendation, very low quality of evidence	2021 Australian Guidelines[5]
After laparoscopic excision or ablation of endometriosis, consider hormonal treatment, to prolong the benefits of surgery and manage symptoms. Clinical judgement and patient preference are factors that may influence the hormonal therapy chosen	Evidence-based recommendation, very low to moderate quality of evidence	2021 Australian Guidelines[5]
Treatment of Endometriosis-Associated Infertility		
Hormone therapy can be offered to women who cannot or decide not to conceive immediately after surgery, as it improves immediate pain outcomes without negatively impacting fertility.	Weak recommendation, Low evidence	ESHRE Guideline: Management of Women with Endometriosis 2022[4]
Offer excision or ablation of endometriosis because this improves the chance of expectant pregnancy. Offer	Evidence-based recommendation, low to moderate	2021 Australian Guidelines[5]

laparoscopic ovarian cystectomy with excision of the cyst wall to people with endometriomas because this improves the chance of expectant pregnancy and reduces recurrence. Consider the person's ovarian reserve.	level of evidence	
Endometriosis and Adolescents		
NSAIDs can be considered for the treatment of endometriosis-associated pain especially if hormone treatment is not an option.	Good Practice Point	ESHRE Guideline: Management of Women with Endometriosis 2022[4]
Hormonal contraceptives or progestogens should be prescribed as first-line hormonal therapy for severe dysmenorrhea and/or endometriosis-associated pain.	Strong recommendation, Very low evidence	ESHRE Guideline: Management of Women with Endometriosis 2022[4]
GnRH agonists may be considered for up to one year in laparoscopically confirmed endometriosis and associated pain since they are safe and effective when combined with add-back therapy.	Weak recommendation, Low evidence	ESHRE Guideline: Management of Women with Endometriosis 2022[4]
Endometriosis and Menopause		
Aromatase inhibitors may be considered for endometriosis-associated pain if surgery is not feasible.	Weak recommendation, Very low evidence	ESHRE Guideline: Management of Women with Endometriosis 2022[4]
Combined menopausal hormone therapy can be considered for symptom relief after natural and/or surgical menopause.	Weak recommendation, Low evidence	ESHRE Guideline: Management of Women with Endometriosis 2022[4]
Avoid estrogen-only regimens for the treatment of vasomotor symptoms due to their possible association with an increased risk of malignant transformation.	Strong recommendation, Low evidence	ESHRE Guideline: Management of Women with Endometriosis 2022[4]

At the end of the report, a key recommendation synthesis section is added highlighting the latest updates in **Endometriosis clinical and therapeutic management**.

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI endometriosis report, and the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This section contains the updated versions of the guidelines mentioned in the May 2020 CHI Endometriosis Report and the corresponding recommendations:

Table 2. Clinical Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated Versions**
Section 1.1 **Endometriosis: diagnosis and management, NICE guideline Published: 6 September 2017**[7]	N/A*
Section 1.2 **The European Society of Human Reproduction and Embryology (ESHRE) guideline: management of women with Endometriosis 2014**	**The European Society of Human Reproduction and Embryology (ESHRE) Guideline: Management of Women with Endometriosis 2022**[4]
Section 1.3 **SOGC CLINICAL PRACTICE GUIDELINE Endometriosis: Diagnosis and Management July 2010**[8]	N/A*
Section 1.4 **American College of Obstetricians and Gynecologists' ACOG COMMITTEE OPINION: Dysmenorrhea and endometriosis in adolescents 2018**[9]	N/A*

*: No updated versions available

1.1.1 Endometriosis: Diagnosis and Management, NICE Guideline (2017)

*Please refer to **Section 1.1** of CHI Endometriosis Report*

There are no new updates. The recommendations of this guideline remain unchanged[7].

1.1.2 The European Society of Human Reproduction and Embryology (ESHRE) Guideline: Management of Women with Endometriosis (2022)

*Please refer to **Section 1.2** of CHI Endometriosis Report*

The 2022 revised edition of the 2014 European Society of Human Reproduction and Embryology (ESHRE) Guideline: Management of Women with Endometriosis has introduced a new set of recommendations accompanied by a grading scheme, outlined as follows[4]:

"Each recommendation was labelled as strong or weak and a grade was assigned based on the strength of the supporting evidence (High ⊕ ⊕ ⊕ ⊕, Moderate ⊕ ⊕ ⊕, Low ⊕ ⊕ and very low ⊕ ⊕). Good practice points (GPPs) based on clinical expertise were added where relevant to clarify the recommendations or to provide further practical advice. 'Research only' recommendations were also made, and those interventions should be applied only within the context of research, with appropriate precautions and ethical approval."

<u>Diagnosis</u>

- Laparoscopy should be offered for the diagnosis and/or treatment of suspected endometriosis in patients "with negative imaging results or where empirical treatment was unsuccessful or inappropriate" (Good Practice Point)
- Identification of endometriotic lesions via laparoscopy is confirmed by histology, although negative histology does not exclude the diagnosis of the disease (Good Practice Point)

<u>Treatment of endometriosis-associated pain</u>

- Analgesics
    - NSAIDs or other analgesics (alone or in combination with other treatments) may be offered (Weak Recommendation, very low evidence)
- Hormone Therapies
    - Combined oral contraceptives, progestogens, GnRH agonists, or GnRH antagonists, are recommended as an option (Strong recommendation, moderate evidence)

- When choosing, clinicians are to take into consideration shared decision-making, patient preferences, side effects, efficacy, costs, and availability (Good Practice Point)
- Combined hormonal contraceptives: (oral, vaginal ring, or transdermal) can be considered to reduce dyspareunia, dysmenorrhea, and non-menstrual pain associated with endometriosis (Strong Recommendation, low evidence)
    - Women who suffer from dysmenorrhea can continuously use a combined hormonal contraceptive pill (Weak recommendation, low evidence)
- Progestogens can be considered (Strong recommendation, low evidence)
    - Clinicians are recommended to take into account the different side effect profiles of progestogens (Good Practice Point)
    - Levonorgestrel-releasing intrauterine (LNG-IUS) system or etonogestrel-releasing subdermal implant is recommended (Strong recommendation, moderate evidence)
- GnRH agonists can be prescribed, although evidence is limited regarding dosage or duration of treatment (Strong recommendation, low evidence)
    - GnRH agonists are prescribed as second-line (e.g., if hormonal contraceptives or progestogens have been ineffective) due to their side effect profile (Good Practice Point)
    - Consider prescribing combined hormonal add-back therapy alongside GnRH agonists to prevent bone loss and hypo-estrogenic symptoms (Strong recommendation, moderate evidence)
- GnRH antagonists can be considered, although evidence is limited regarding dosage or duration of treatment (Weak Recommendation, moderate evidence)
    - GnRH antagonists are prescribed as second-line (e.g., if hormonal contraceptives or progestogens have been ineffective) due to their side effect profile (Good Practice Point)
- Aromatase Inhibitors are recommended for pain refractory to medical/surgical treatment, and may be given in combination with oral contraceptives, progestogens, GnRH agonists, or GnRH antagonists (Strong recommendation, low evidence)

- When choosing between hormone treatments and surgical treatments, clinicians are recommended to take a shared decision-making approach, considering individual preferences, side effects, efficacy, costs, and availability (Good Practice Point)
- Surgery
    - In women who have failed to respond to conservative treatments and do not wish to conceive, consider hysterectomy with the removal of all visible lesions (with or without removal of the ovaries). Patients should be informed that it will not necessarily cure the disease or its symptoms (Weak recommendation, low level of evidence)
    - When a decision regarding the removal of ovaries is made, consider the long-term consequences of early menopause and the possible need for hormone replacement therapy. (Good Practice Point)
    - A total hysterectomy is preferred (Good Practice Point)
- Medical Therapies as Adjunct to Surgery
    - Preoperative hormone treatment is not recommended to improve immediate pain outcome (Strong Recommendation, low evidence)
    - Postoperative hormone treatment may be recommended to improve immediate pain outcome if not desiring immediate pregnancy (Weak recommendation, low evidence)
- Non-Medical Management Strategies
    - Address quality of life and psychological well-being but no recommendations can be made for any specific non-medical intervention (Chinese medicine, nutrition, electrotherapy, acupuncture, physiotherapy, exercise, and psychological interventions) to reduce pain or improve quality of life measures since the potential harms and benefits are unclear (Good Practice Point)

<u>Treatment of endometriosis-associated infertility</u>

- Hormone/Medical Therapies
    - Ovarian suppression therapy should not be prescribed (Strong recommendation, low evidence)
    - Postoperative hormone suppression should not be recommended for the sole purpose of enhancing future pregnancy rates (Strong recommendation, low evidence)
    - Hormone therapy can be offered to women who cannot attempt or who decide not to conceive immediately after surgery, as it improves

immediate pain outcomes and does not negatively impact their fertility (Weak recommendation, low evidence)

  - Pentoxifylline, other anti-inflammatory drugs, or letrozole, should not be prescribed outside ovulation-induction to improve natural pregnancy rates (Strong recommendation, very low evidence)

- Medically Assisted Reproduction
  - A specific protocol for ART cannot be recommended. Both GnRH antagonist and agonist protocols can be offered based on patients' and physicians' preferences as no difference in pregnancy or live birth rate has been demonstrated (Weak recommendation, very low evidence)
- Medical Therapies as an Adjunct to Medically Assisted Reproduction
  - The extended administration of GnRH agonist prior to ART treatment is not recommended to improve live birth rate, as the benefit is uncertain (Strong recommendation, very low evidence)
  - Evidence is insufficient to recommend prolonged COC/progestogen administration as ART pre-treatment to increase live birth rates (Weak recommendation, very low evidence)
- Impact of Endometriosis on Pregnancy and Obstetric Outcomes
  - Patients are not to become pregnant with the sole purpose of treating endometriosis since this does not always lead to symptom improvement or reduction in disease progression (Strong recommendation. Very low evidence)
  - The appearance of endometriosis may change during pregnancy. The patient is to be referred to an appropriate center with expertise in case atypical endometrioma was present during an ultrasound in pregnancy (Strong recommendation, very low evidence)
  - Clinicians should be aware that women in the first trimester are at an increased risk of miscarriage and ectopic pregnancy (Strong recommendation, low evidence)
  - Although rare, clinicians should be aware of pregnancy complications. These results should be cautiously interpreted since the studies are of low/moderate quality. They currently do not warrant increased antenatal monitoring or dissuade women from becoming pregnant. (Strong recommendation, low evidence)
- Endometriosis Recurrence
  - For secondary prevention of dysmenorrhea, dyspareunia, and non-menstrual pelvic pain, ovarian cystectomy should be performed when

surgery is indicated instead of drainage and electrocoagulation. The risk of the ovarian reserve should be considered (Strong recommendation, low evidence)

    - For the secondary prevention of dysmenorrhea, clinicians should consider an LNG-IUS system (52mg) or combined hormonal contraceptive for at least 18-24months for postoperative use (Strong recommendation, low evidence)
    - For the secondary prevention of endometrioma and endometriosis-related symptom recurrence, and after surgical management of ovarian endometrioma in women not seeking immediate conception, long-term hormone treatment can be offered (such as combined hormonal contraceptives) (Strong recommendation, very low evidence)
    - Long-term postoperative hormone treatment can be considered to prevent the recurrence of deep endometriosis (and associated symptoms) (Weak recommendation, very low evidence)
    - ART can be performed in deep endometriosis since it does not seem to increase endometriosis recurrence (Weak recommendation, moderate evidence)

- Reoccurring Endometriosis or Recurring Symptoms
    - Any hormone treatment or surgery can be offered (Weak recommendation, very low evidence)

<u>Endometriosis and Adolescence</u>

- Treatment for (suspected) endometriosis in adolescents
    - If severe dysmenorrhea and/or endometriosis-associated pain, hormonal contraceptives, or progestogens (systemic or LNG-IUS) should be prescribed as first-line hormonal therapy due to their safety and effectiveness. On the other hand, it is important to note that some progestogens may decrease bone mineral density (Strong recommendation, very low evidence)
    - In patients with (suspected) endometriosis, NSAIDs are to be considered for the treatment of endometriosis-associated pain, especially if first-line hormone treatment is not an option (Good Practice Point)
    - In laparoscopically confirmed endometriosis and associated pain, where hormonal contraceptives or progestogen therapy had failed, GnRH agonists may be considered for up to one year, due to their

safety and effectiveness when combined with add-back therapy (Weak recommendation, low evidence)

- If GnRH agonist treatment is considered, a practitioner in a secondary or tertiary care setting is to use careful consideration, along with a discussion of potential side effects and long-term health risks. (Good Practice Point)
- Surgical removal of endometriosis lesions may be considered to manage symptoms. Nevertheless, symptom recurrence rates may be considerable, especially when surgery is not followed by hormone treatment (Weak recommendation, very low evidence)
- If surgical treatment is indicated, it is to be performed "laparoscopically by an experienced surgeon, and, if possible, complete laparoscopic removal of all present endometriosis should be performed" (Good Practice Point)
- Consider postoperative hormonal therapy since it may suppress symptom recurrence (Strong recommendation, very low evidence)

<u>Endometriosis and Menopause</u>

- Medical Treatment recommendations
  - For endometriosis-associated pain, and if surgery is not a feasible treatment option, clinicians may consider aromatase inhibitors (Weak recommendation, very low evidence)
  - After natural and/or surgical menopause, combined menopausal hormone therapy can be considered for symptom relief (Weak recommendation, low evidence)
  - Avoid estrogen-only regimens for the treatment of vasomotor symptoms due to their possible association with an increased risk of malignant transformation (Strong recommendation, low evidence)
  - After surgical menopause, patients should continue treatment with combined estrogen-progestogen, at least up until the age of natural menopause (Good Practice Point)

<u>Extra-pelvic Endometriosis</u>

- Treatment recommendations
  - In abdominal extra-pelvic endometriosis, the preferred treatment for symptom relief is surgical removal. If not possible or unacceptable, hormone treatment is an alternative option. (Weak recommendation, very low evidence)

    - In thoracic endometriosis, hormone treatment may be an option. In cases where surgery is indicated, it is to be performed in a multidisciplinary manner (specialists, including a thoracic surgeon) (Weak recommendation, very low evidence)

Asymptomatic Endometriosis Women should be informed and counseled on any incidental finding of endometriosis (Good Practice Point)

- Surgical excision/ablation for incidental findings of asymptomatic endometriosis at the time of surgery is not routinely performed (Strong recommendation, very low evidence)
- Medical treatment is not to be prescribed for women with incidental findings of endometriosis (Strong recommendation, very low evidence)
- Consider routine US monitoring of asymptomatic endometriosis (Weak recommendation, very low evidence)

Primary Prevention of Endometriosis

- The advice is to aim for a healthy lifestyle and diet: with reduced alcohol intake and regular physical activity (Weak recommendation, low evidence)
- The usefulness of hormonal contraceptives is uncertain (Weak recommendation, low evidence)
- Genetic testing should only be performed in a research setting (Research-only)

Endometriosis and Cancer

- Women with endometriosis who are questioning their risk of cancer are to be informed that endometriosis is not associated with a significantly higher risk overall. Compared to women in the general population, the increase in absolute risk of ovarian, breast, and thyroid cancer is low- despite being associated with a higher risk. (Strong recommendation, low evidence)
- Clinicians are to reassure their patients about their cancer risk and address their common concerns. They are also to recommend general prevention measures such as “avoiding smoking, maintaining a healthy weight, exercising regularly, having a balanced diet with high intakes of fruits and vegetables and low intakes of alcohol, and using sun protection”. (Good Practice Point)
- “Clinicians should be aware that there is epidemiological data, mostly on ovarian endometriosis, showing that complete excision of visible endometriosis may reduce the risk of ovarian cancer.” The potential benefits and risks of surgery should be weighed (Strong recommendation, low evidence)

- The potential benefits should be weighed against the risks of surgery (morbidity, pain, and ovarian reserve)

1.1.3 SOGC Clinical Practice Guideline Endometriosis: Diagnosis and Management (2010)

*Please refer to **Section 1.3** of CHI Endometriosis Report*

There are no new updates. The recommendations of this guideline remain unchanged[8].

1.1.4 American College of Obstetricians and Gynecologists ACOG COMMITTEE OPINION: Dysmenorrhea and Endometriosis in Adolescents (2018)

*Please refer to **Section 1.4** of CHI Endometriosis Report*

There are no new updates. The recommendations of this guideline remain unchanged[9].

1.2 Additional Guidelines

This section includes the added guidelines to the previous CHI Endometriosis report, along with their recommendations.

Table 3. List of Additional Guidelines

Additional Guidelines
Clinical practice guidelines for Endometriosis in Japan (The 3rd edition) (2022)[6]
Australian clinical practice guideline for the diagnosis and management of endometriosis (2021)[5]

1.2.1 Clinical Practice Guidelines for Endometriosis in Japan (The 3rd edition) (2022)

Evidence levels and recommendation grades are outlined below:

Table 4. Grading Scheme for Recommendations

Grading Scheme for Recommendations	
Evidence Level	I → Systematic Review/Meta-analysis II → 1 or more RCTs III → non-RCT

	IV → Clinical Trial/Cohort Study V → Descriptive Study VI → Not based on patient data, or opinion of expert panel or individual expert
Recommendation Grade	A → Strongly recommended. B → Recommended C → Recommended, but no clear evidence D → Not recommended

The following recommendations are provided by the 2022 Japanese Clinical Guidelines on the management of endometriosis[6].

A suitable regimen for endometriosis therapy involves the combination of medical and surgical therapy, in addition to ART in infertile patients.

Medical therapy: consists of symptomatic treatment (analgesics and Chinese herbal medicine) and hormone therapy.

- NSAIDs are the first-line analgesics in cases of severe menstrual pain, in unmarried women: starting from adolescence up to their twenties.
- Chinese Herbal Medicine is used for the relief of menstrual pain in unmarried and adolescent women and is associated with less adverse effects with respect to other drugs. These agents include:
    - shakuyakukanzoto (peony and licorice decoction)
    - tokishakuyakusan (angelica and peony powder)
    - keishibukuryogan (cassia twig and tuckahoe pill)
    - tokakujokito (peach kernel purgative decoction)

- Treatment flowchart for patients with pain is found below:

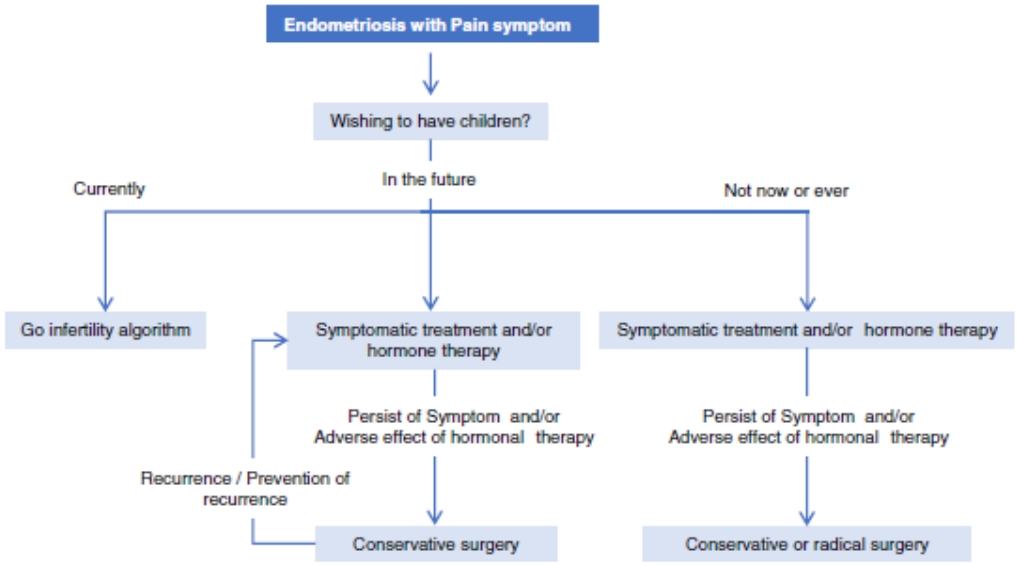

Figure 1. *Treatment of Endometriosis: Flowchart for Patients with Pain. Retrieved from Harada T, Taniguchi F, Kitajima M, et al. Clinical practice guidelines for endometriosis in Japan (The 3rd edition). J Obstet Gynaecol Res. 2022;48(12):2993-3044. doi:10.1111/jog.15416.*

- Hormone therapy:
    - OCs/LEPs are first-line treatment options. If not sufficiently effective, GnRH agonists are an alternative option.
    - LNG-IUS is also sometimes used.
    - The use of Danazol has declined in recent years.
    - Progestins:
        - Dydrogesterone is used for luteal support in fertility treatment and in postmenopausal hormone replacement therapy. Its use has declined following the use of danazole and GnRH agonists.
        - LNG-IUS prevents the recurrence of dysmenorrhea.

Surgical therapy is considered when medical therapy fails to inhibit pain sufficiently.

- Postoperative hormone therapy is considered to prevent decreased ovarian reserve from repeated surgeries (since ovarian endometriotic cysts frequently recur after conservative surgery)
- OCs/LEPs and dienogest are effective in the prevention of ovarian endometriotic cyst recurrence postoperatively. Six months of GnRH agonist administration followed by continuous OC/LEP/ dienogest, is effective to prevent postoperative recurrence.
- Management after conservative therapy:

    - Preventative long-term administration of OC/LEP combinations has been reported to reduce recurrence and inhibit pain.
    - Dienogest for postoperative recurrence has reduced the need for repeat surgeries.
- Management after radical surgery:
    - Dienogest or other medical therapy are considered in cases of pelvic pain where deep lesions persist despite hysterectomy and removal of foci.
    - If ovaries are removed, estrogen replacement therapy (ERT) is initiated to relieve ovarian deficiency symptoms and prevent low-estrogen bone loss.

Adolescents with suspected endometriosis:

- Analgesics and hormone preparations are recommended (IA)
- If ineffective or if there is obstruction in the reproductive tract, surgery is to be performed (IIIC)
- Hormone preparations after surgery are to be prescribed to prevent progression and recurrence (IIIC)

Adenomyosis-associate pain and infertility:

- Similar medical therapy as that of endometriosis is to be considered (IB)
- “A higher likelihood of achieving pregnancy can be expected by GnRH agonists followed by ART” (IIIC)

Cardiovascular event risks:

- “Endometriosis is suggested to be a risk factor for future angina, myocardial infarction, and cerebral infarction” (N/a III)

Quality of Life

- Endometriosis negatively affects quality of life, but it may be improved by medical and surgical treatment (IA)

Endometriosis-associated infertility:

- There is no evidence that hormone therapy is effective (ID)
- More research is needed to know if hormone therapy is effective prior to ART (IC).

Endometriosis-associated pain:

- OCs/LEPs are effective in reducing pain (IB)
- GnRH agonists are also effective in reducing pain (IB)
- Dienogest is also effective in reducing pain (IB)
- LNG-IUS is also effective in reducing pain (IB)
- They are equivalent in their pain reduction effects (IB)
- There are no reliably effective complementary or alternative therapies (IIC)
- The evidence is not enough to recommend preoperative medical therapy to improve surgical results in reducing pain (IIC)
- Long-term medical therapy after surgery has been shown to be effective in preventing pain recurrence. Short-term therapy has not been shown to be effective (IA)

Deep endometriosis-associated pain:

- Norethisterone, LNG-IUS, dienogest, and GnRH agonists are all effective (IIB)

Preventing recurrence of ovarian endometriotic cysts:

- Administration of long-term OC/LEP combinations is effective (IIB)
- There is no evidence that LNG-IUS reduces the recurrence of ovarian endometriotic cysts (IIB)
- Long-term dienogest administration may reduce their recurrence (IVC)

1.2.2 Australian Clinical Practice Guideline for the Diagnosis and Management of Endometriosis (2021)

Evidence levels and recommendation grades are outlined below[5]:

Table 5. Australian Guideline Types of Recommendations

Type of Recommendation	Definition
Evidence-based recommendation	Recommendation formulated with evidence from source guideline and/or new literature searches
Consensus-based recommendation	Recommendation formulated by consensus, where evidence was sought but none was identified, or the identified evidence was limited by indirectness
EEWG Opinion	Guidance that is outside the scope of the evidence search and is based on consensus of the Endometriosis Expert Working Group (EEWG)

Table 6. Australian Guideline Quality of Evidence

Quality of Evidence	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very Low	An estimate of effect is very uncertain

The following recommendations are provided by the 2021 Australian clinical practice guideline for the diagnosis and management of endometriosis[5]:

Signs and symptoms of endometriosis:

- Suspect endometriosis in patients presenting with one or more of the following: persistent pelvic pain, period-related pain (dysmenorrhea) affecting daily activities and quality of life, deep pain during/after sexual intercourse, period-related or cyclical GI or urinary symptoms (painful bowel movements or blood in the urine/pain passing urine), and infertility associated with one or more of the above (Evidence-based recommendation, moderate quality of evidence)
- Keeping a pain and symptom dairy can aid discussions in people with suspected or confirmed endometriosis (Consensus-based recommendation)
- To identify abdominal masses and pelvic signs (reduced organ mobility and enlargement, tender nodularity in the posterior vaginal fornix, visible vaginal endometriotic lesions), offer abdominal and pelvic examination in suspected endometriosis patients (Consensus-based recommendation)
- Offer an abdominal exam to exclude abdominal masses if a pelvic examination is not appropriate in people with suspected endometriosis (Consensus-based recommendation)

Information and support for endometriosis patients

- Spread awareness that endometriosis is a long-term condition that may have significant impacts physically, sexually, psychosocially, and socially. Endometriosis patients may have complex needs and may require long-term support (Evidence-based recommendation, low-moderate quality of evidence)

- Assess individual information and support the needs of suspected/confirmed endometriosis patients, considering different factors such as circumstances, symptoms, co-existing conditions, priorities/fertility desire, daily living constraints, cultural background, and emotional/physical/psychosexual needs (Evidence-based recommendation, low-moderate quality of evidence).
- Provide constant support such as comprehensive and ongoing information to suspected/confirmed endometriosis patients, to promote their active involvement in care and self-management. (Consensus-based recommendation)
- With the patient's agreement, involve the people important to them, such as family members or partner, and include them in discussions (consensus-based recommendation)
- Offer consultation and investigate options for suspected/confirmed endometriosis patients who reside in rural and remote areas. Make telehealth consultations available and prioritize access to imaging services in rural and remote areas. These services should be equitable to those in metropolitan centers (EEWG Opinion recommendation).

Prompt diagnosis of endometriosis and early intervention

- Community, gynecology, and specialist endometriosis services should provide coordinated care for suspected/confirmed endometriosis patients (Consensus-based recommendation)
- Offer comprehensive coordinated care to patients with suspected/confirmed endometriosis, and have processes in place for prompt diagnosis and treatment of this condition since any delay can affect quality of life and lead to disease progression (Consensus-based recommendation)
- A GP chronic disease management plan can help access appropriate assessment and access to services (EEWG Opinion recommendation)

Organization of Care

- Set up a managed clinical network for people with suspected/confirmed endometriosis, comprising of community services (general practitioners, practice nurses, school nurses and sexual health services), gynecology services, and specialist endometriosis services (endometriosis centers) (Consensus-based recommendation)
- Patients with suspected or confirmed endometriosis may require access to a gynecologist with expertise in diagnosing/managing endometriosis, a gynecology specialist nurse with expertise in endometriosis, a

multidisciplinary pain management service, a healthcare professional with an interest in gynecological imaging, and./or fertility services (Consensus-based recommendation).

- Patients with suspected or confirmed deeply infiltrating endometriosis may require additional access to gynecologists with expertise in diagnosing and managing endometriosis, including advanced laparoscopic surgical skills, a colorectal surgeon with interest in endometriosis, a urologist with interest in endometriosis, an endometriosis specialist nurse, a multidisciplinary pain management service with expertise in pelvic pain, a healthcare professional with specialist expertise in gynecological imaging of endometriosis, advanced diagnostic facilities (radiology and histopathology), and/or fertility services (Consensus-based recommendation).

Referral of people with endometriosis to secondary care

- Consider referring people with suspected/confirmed endometriosis to a gynecologist if the ultrasound/imaging are suggestive of a higher stage or deeply infiltrating disease (endometriosis, adenomyosis, or disease invading other organs), they have severe, persistent, or recurrent symptoms of endometriosis, they have signs of endometriosis on examination, or initial management is not effective, not tolerated, or contraindicated (Consensus-based recommendation).
- Refer people with suspected or confirmed endometriosis to a gynecologist with an interest in endometriosis if they have suspected or confirmed deep endometriosis involving the bowel, bladder, or ureter (Consensus- based recommendation)
- Consider referring young people (17 years of age and younger) with suspected or confirmed endometriosis to a pediatric and adolescent gynecologist with an interest in endometriosis depending on local service provision, or to a gynecologist who is comfortable treating adolescent with possible endometriosis (consensus-based recommendation)

Interdisciplinary care to manage endometriosis

- Gynecologists may consider multidisciplinary input to manage people with endometriosis, where: (EEWG Opinion)
    - Bladder, bowel, ureter involvement is suspected based on history, examination, or investigations.
    - Medical or surgical treatments have failed to improve symptoms.
    - Musculoskeletal or neuropathic contributions to pain are suspected.

    - Pain affects daily functioning.
    - They are diet and bowel related issues.
    - There are mental health and social impacts.

Diagnosis of endometriosis

- A normal abdominal or pelvic examination, ultrasound, CT, or MRI does not exclude the possibility of endometriosis. If clinical suspicion remains or symptoms persist, consider referral for further assessment and investigation (Evidence-based recommendation, very low quality of evidence).
- Clinical examination: a clinical pelvic exam is an important part of an initial assessment to investigate suspected endometriosis- consider offering a pelvic exam, or an abdominal exam if not appropriate (evidence-based recommendation, very low quality of evidence)
- Ultrasound:
    - Consider transvaginal ultrasound to investigate suspected endometriosis even if the pelvic and/or abdominal exam is normal, and/or to identify endometriosis (evidence-based recommendation, very low quality of evidence)
    - Consider specialized US to assess the extent of deep endometriosis involving the bowel, bladder, or ureter (evidence-based recommendation, very low quality of evidence)
    - Specialized US scans are best interpreted by a healthcare professional with a specialist expertise in gynecological imaging (consensus-based recommendation)
    - If a transvaginal scan is not appropriate, consider transabdominal US scan of the pelvis (consensus-based recommendation)
- Biomarkers:
    - Do not use serum CA125 to diagnose endometriosis (evidence-based recommendation, very low quality of evidence)
    - If a coincidentally reported serum CA125 level is available, be aware that: a raised serum CA125 (35IU/mL or more) may be consistent with having endometriosis, and that endometriosis may be present despite a normal serum CA125 (less than 35 IU/mL) (Evidence-based recommendation, very low quality of evidence)

- Magnetic Resonance Imaging (MRI)
    - Do not use pelvic MRI as the primary investigation to diagnose endometriosis in people with signs or symptoms suggestive of endometriosis (evidence-based recommendation, very low quality of evidence)
    - Consider pelvic MRI to assess the extent of deep endometriosis involving the bowel, bladder, or ureter (evidence-based recommendation, very low quality of evidence)
    - Pelvic MRI scans are best interpreted by a healthcare professional with specialist expertise in gynecological imaging (consensus-based recommendation)
- Computed Tomography (CT)
    - Do not use CT scanning as the primary investigation to diagnose endometriosis in people with signs or symptoms suggestive of endometriosis (evidence-based recommendation, very low quality of evidence)
    - CT scanning may be used to assess the extent of deep endometriosis involving the bowel, bladder, or ureter if MRI is not accessible (evidence-based recommendation, very low quality of evidence)
    - CT scans are best interpreted by a healthcare professional with specialist expertise in gynecological imaging (consensus-based recommendation)
- Laparoscopy- surgical diagnosis
    - Consider laparoscopy to diagnose and treat people with suspected endometriosis, even if the ultrasound is normal (evidence-based recommendation, very low quality of evidence)
    - For people with suspected deep endometriosis involving the bowel, bladder, or ureter, consider a detailed pelvic ultrasound or MRI before operative laparoscopy (evidence-based recommendation, very low quality of evidence)
    - During a laparoscopy for suspected endometriosis, a gynecologist with training and skills in laparoscopic surgery for endometriosis should perform a systematic inspection of the pelvis and abdomen (consensus-based recommendation)
    - During a laparoscopy where there is apparent endometriosis, consider a biopsy to confirm the diagnosis of endometriosis (noting that a negative history result does not exclude endometriosis), to exclude

malignancy if an endometrioma is treated but not excised, and where there are indeterminant lesions, avoid missing the opportunity to diagnose endometriosis (evidence-based recommendation, very low quality of evidence)

- If a full, systematic laparoscopy is performed and no endometriosis is found, explain to the person that endometriosis was not identified, and offer management of persistent symptoms (evidence-based recommendation, very low quality of evidence)

Diagnosis of adenomyosis

- Consider US for the diagnosis because it may provide useful information, even though features are variable and diagnostic performance is limited by the lack of agrees diagnostic criteria (evidence-based recommendation, very low quality of evidence)
- Do not use MRI as a first-line method to diagnose adenomyosis, however MRI may be appropriate for specific situations (consensus-based recommendation)

Factors that can guide treatment of endometriosis

- Offer treatment according to the person's symptoms, preferences, and priorities, rather than the stage of endometriosis. Treatment should be patient-focused considering the person's physical, psychological, sexual, social, spiritual, and cultural needs and preferences (consensus-based recommendation)
- When endometriosis is diagnosed, the gynecologist should document a detailed description of the appearance and site of endometriosis. These documentations should be in line with the data dictionary developed by the National Endometriosis Clinical and Scientific Trials (NECST) Network (consensus-based recommendation).

Pharmacological management of pain associated with endometriosis/adenomyosis using analgesics

- Consider a short trial (3 months) of a non-steroidal anti-inflammatory drug (NSAID) alone or in combination with paracetamol, if not contraindicated. If such a trial does not provide adequate pain relief, consider other forms of pain management and referral for further assessment (consensus-based recommendation)

Pharmacological management of pain associated with endometriosis using anti-neuropathic medications

- Advise people that there is no evidence for or against the use of anti-neuropathic medications for pain associated with endometriosis (consensus-based recommendation)
- People with endometriosis should be referred to a pain specialist and/or a condition-specific specialist at any stage if pain is severe and unresponsive to simple analgesics, the pain substantially limits daily activities, or any underlying health condition has deteriorated (consensus-based recommendation)

Pharmacological management of endometriosis using hormonal medical treatments

- Explain to people with suspected of confirmed endometriosis that hormonal treatment can reduce pain and has no permanent negative effect on subsequent fertility (other than delaying the time to fertility, which may be important, depending on the person's age) (evidence-based recommendation, moderate quality of evidence)
- Offer hormonal treatment (combined oral contraceptive pill or a progestogen as an oral form, a subcutaneous implant of intrauterine device form) to people with suspected, confirmed, or recurrent endometriosis. The choice of hormonal treatment should be in a shared decision-making approach, recognizing that no hormonal treatment has been demonstrated to be superior (evidence-based recommendation, moderate quality of evidence)
- If initial hormonal treatment for endometriosis is not effective, not tolerated or contraindicated, refer the person to a gynecologist for investigation and treatment options, based on the person's preferences (consensus-based recommendation)
- As an adjunct to surgery for deep endometriosis involving the bowel, bladder, or ureter, consider 3 months of gonadotropin-releasing hormone (GnRH) agonists before surgery (consensus-based recommendation)

Pharmacological management of adenomyosis using hormonal medical treatments

- Explain to people with suspected of confirmed adenomyosis that hormonal treatment can reduce pain and has no permanent negative effect on subsequent fertility (other than delaying the time to fertility, which may be important, depending on the person's age) (evidence-based recommendation, low quality of evidence)

- Offer hormonal treatment (combined oral contraceptive pill or a progestogen as an oral form, a subcutaneous implant of intrauterine device form) to people with suspected, confirmed, or recurrent adenomyosis. The choice of hormonal treatment should be in a shared decision-making approach, recognizing that no hormonal treatment has been demonstrated to be superior (evidence-based recommendation, low quality of evidence)
- If initial hormonal treatment for adenomyosis is not effective, not tolerated or contraindicated, refer the person to a gynecologist for investigation and treatment options, based on the person's preferences (consensus-based recommendation)

Non-pharmacological and non-surgical managements for pain associated with endometriosis

- Advise people that there is no evidence to support the use of Chinese herbal medicines or supplements for treating endometriosis, and that there are concerns related to potential harms associated with their use (evidence-based recommendation, low quality of evidence)
- Advise people that there is limited evidence on the effectiveness of acupuncture for the management of endometriosis pain (evidence-based recommendation, very low to moderate quality of evidence)

Non-pharmacological and non-surgical managements for pain associated with adenomyosis

- Advise people with adenomyosis who are considering using non-pharmacological or non-surgical management for pain associated with adenomyosis that there is little to no evidence to support their use (consensus-based recommendation)

Surgical management of endometriosis

- Discuss surgical management options with people with suspected or confirmed endometriosis, covering what surgery involves, that surgery may include treatment of lesions (with prior patient consent), how surgery could affect endometriosis symptoms, the possible benefits and risks of surgery, the possible need for further surgery (for example, for recurrent endometriosis or if complications arise), and the possible need for further planned surgery for deep endometriosis involving the bowel, bladder, or ureter (evidence-based recommendation, very low quality of evidence)

- If surgery is performed for endometriosis, it should be performed by laparoscopy rather than laparotomy, unless there are contraindications (evidence-based recommendation, very low quality of evidence)
- Consider cyst excision rather than cyst ablation to treat endometriosis, considering the person's desire for fertility, previous ovarian surgery, and ovarian reserve (evidence-based recommendation, very low to low quality of evidence)
- Deeply infiltrating endometriosis with side-wall disease, bowel or bladder involvement increases surgical complexity and may increase the risk of complications. Referral to one or more clinicians with appropriate skills to address this disease is advised (EEWG Opinion recommendation)

Surgical management of adenomyosis

- Advise people contemplating excisional or ablative surgery for the treatment of adenomyosis that there is no evidence for or against such surgery in the treatment of adenomyosis.

Combination of surgery and hormonal treatment for endometriosis

- After laparoscopic excision or ablation of endometriosis, consider hormonal treatment, to prolong the benefits of surgery and manage symptoms. Clinical judgement and patient preference are factors that may influence the hormonal therapy chosen (evidence-based recommendation, very low to moderate quality of evidence)

Combination of surgery and hormonal treatment for adenomyosis

- Adenomyosis is a condition that is usually treated with either hormonal therapy or surgery (adenomyectomy or hysterectomy), rather than combined hormonal and surgical therapies. Hormonal therapy may be offered as a first-line treatment for adenomyosis depending upon clinical judgement and patient preference. Surgical options are limited if fertility is to be preserved (consensus-based recommendation)

Hysterectomy for the management of endometriosis

- Advise people contemplating a hysterectomy that there is no evidence for or against its effectiveness in endometriosis. If indicated (if the person has adenomyosis or heavy menstrual bleeding that has not responded to other treatments), all visible endometriotic lesions should be excised at the time of the hysterectomy (consensus-based recommendation)

- For people with endometriosis who are thinking about having a hysterectomy, discuss what it involves and when it may be needed, the possible benefits and risk of a hysterectomy, or of having oophorectomy at the same time as a hysterectomy, how a hysterectomy could affect endometriosis symptoms, that hysterectomy should be combined with excision of all visible lesions, that it may recure with the possible need for further surgery, and the possible benefits and risks of menopausal hormone therapy after hysterectomy with oophorectomy (consensus-based recommendation)
- When hysterectomy is combined with surgical treatment of endometriosis, perform the hysterectomy with/without oophorectomy laparoscopically unless there are contraindications (consensus-based recommendation)

Hysterectomy for the management of adenomyosis

- Advise people contemplating a hysterectomy that there is no evidence for or against its effectiveness in adenomyosis-associated pain. Women who have heavy menstrual bleeding will have resolution of their heavy menstrual bleeding (consensus-based recommendation)
- For people with endometriosis who are thinking about having a hysterectomy, discuss what it involves and when it may be needed, the possible benefits and risk of a hysterectomy, or of having oophorectomy at the same time as a hysterectomy, how a hysterectomy could affect adenomyosis symptoms, that hysterectomy should be combined with excision of all visible endometriotic and adenomyotic lesions, and the possible benefits and risks of menopausal hormone therapy after hysterectomy with oophorectomy (consensus-based recommendation)

Management strategies to enhance fertility in people with endometriosis

- The management of endometriosis-related infertility should involve an interdisciplinary team that includes a specialist with a specific interest in fertility associated with endometriosis. This should include the recommended diagnostic fertility tests or preoperative tests, as well as other recommended fertility treatments, such as assisted reproduction (EEWG opinion)
- For people who are trying to conceive, discuss the benefits and risks of laparoscopic surgery as a treatment option (working with a specialist with an interest in fertility associated with endometriosis). Topics may include whether laparoscopic surgery may alter the chance of future pregnancy, the possible impact on ovarian reserve, the possible impact on fertility if complications arise, alternatives to surgery, other fertility factors, and non-fertility related benefits, such as pain management (evidence-based recommendation, low to moderate quality of evidence)

- Offer excision or ablation of endometriosis because this improves the chance of expectant pregnancy. Offer laparoscopic ovarian cystectomy with excision of the cyst wall to people with endometriomas because this improves the chance of expectant pregnancy and reduces recurrence. consider the person's ovarian reserve (evidence-based recommendation, low to moderate level of evidence)
- Do not offer hormonal suppression treatments to people with endometriosis who are trying to conceive, because it does not improve expectant pregnancy rates (evidence-based recommendation, low to moderate quality of evidence)

Follow-up of asymptomatic endometriosis

- Consider follow-up (with or without examination and pelvic imaging) for people with confirmed but asymptomatic endometriosis, particularly those who choose not to have surgery, if they have deeply infiltrating endometriosis involving the bowel, bladder, or ureter, or if 1 or more endometrioma that are larger than 3 cm (consensus-based recommendation)

Secondary prevention of endometriosis

- Prophylactic surgery is not recommended in the absence of symptoms, given the lack of evidence and potential for surgical complications (consensus-based recommendation)

Risk of cancer of the reproductive organs in people with endometriosis

- People may be concerned that endometriosis is associated with an increased risk of cancer of the reproductive organs. Be aware of these concerns, and that there is no conclusive evidence to support such an association (EEWG opinion)

Section 2.0 Drug Therapy in Endometriosis

This section comprises four subsections: the first contains the newly recommended drugs, the second covers drug modifications, the third outlines the drugs that have been withdrawn from the market, and the fourth details drugs that have newly been approved by the FDA and/or EMA but have not yet been registered by the SFDA.

2.1 Additions

There are no new drugs added to the treatment of endometriosis. The drugs used in the management of endometriosis are still the same.

2.2 Modifications

The European Society of Human Reproduction and Embryology (ESHRE) guideline: management of women with Endometriosis 2022

- Extended GnRH agonist administration before ART is no longer recommended.
- Danazol and anti-progestogens are no longer recommended.

2.3 Delisting

The medications below are no longer SFDA registered[10], therefore, it is advisable to delist the following drugs from CHI formulary. *Please refer to* ***Drug Therapy in Endometriosis- Section 2*** *of CHI Endometriosis original clinical guidance*

- Acemetacin
- Estradiol Hemihydrate, Drospirenone
- Ethinylestradiol, Norgestimate

2.4 Other Drugs

Myfembree® (relugolix, estradiol and norethindrone acetate)

Originally approved by the FDA in May 2021 for the treatment of heavy menstrual bleeding associated with uterine fibroids, it was also approved in August 2022 for the management of moderate to severe pain associated with endometriosis.

Approval was based on two replicate phase 3 trials (SPIRIT 1 and 2), which showed that once-daily relugolix combination therapy significantly improved endometriosis-associated pain and was well tolerated[11].

Section 3.0 Key Recommendations Synthesis

- Nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended as first-line analgesics for severe menstrual pain (ESHRE 2022[4] Guidelines: Weak Recommendation, very low evidence).
- Chinese Herbal Medicine: Shakuyakukanzoto and tokishakuyakusan can be used for menstrual pain relief in unmarried and adolescent women (2018 ACOG Committee Opinion[9], No level of recommendation in 2022 Japanese guideline[6]).
- Hormone therapies: combined oral contraceptives (OCs), levonorgestrel-releasing intrauterine systems (LNG-IUS), gonadotropin-releasing hormone (GnRH) agonists, and progestins such as dydrogesterone (Strong recommendation, moderate evidence in 2022 ESHRE Guidelines[4], Level IB recommendation in 2022 Japanese guidelines[6]).
- Nonpharmacologic options in adolescents include interventions like applying heat, engaging in exercise, practicing relaxation techniques, and promoting a healthy lifestyle while emphasizing stress management. (ACOG Committee Opinion, 2018[9])
- Surgical therapy: when medical therapy fails to sufficiently control pain. Options may include the removal of endometriotic lesions through laparoscopy. Postoperative hormone therapy can be used to prevent recurrence of ovarian endometriotic cysts, and long-term administration of OCs/LEPs (combined oral contraceptives or levonorgestrel-releasing intrauterine systems) and dienogest may help prevent postoperative recurrence (Weak recommendation, low evidence in 2022 ESHRE Guidelines[4], Level IA recommendation in 2022 Japanese guidelines[6]).
- Adolescents with suspected endometriosis: Analgesics and hormone preparations are recommended (Strong recommendation, very low evidence in 2022 ESHRE Guidelines[4]). Surgery should be considered if medical therapy was ineffective or if there is reproductive tract obstruction (Weak recommendation, very low evidence in 2022 ESHRE Guidelines[4]). Hormone preparations after surgery should be prescribed to prevent progression and recurrence (Strong recommendation, very low evidence in 2022 ESHRE Guidelines[4], Level IIIC recommendation 2022 Japanese guidelines[6]).
- Aromatase inhibitors: Can be considered for endometriosis-associated pain, particularly in the context of menopause (Strong recommendation, low evidence in 2022 ESHRE Guidelines[4], 2017 NICE[7]).

- Endometriosis and Menopause: Combined menopausal hormone therapy can be considered for symptom relief after natural or surgical menopause, avoiding estrogen-only regimens (Good Practice Point in 2022 ESHRE Guidelines[4]).
- Treatment of Endometriosis-associated Infertility in 2022 ESHRE Guidelines[4]: Ovarian suppression therapy should not be prescribed (Strong recommendation, low evidence). Medically assisted reproduction can be considered, and specific protocols are based on patient and physician preferences (weak recommendation, very low evidence). Hormone therapies as an adjunct to medically assisted reproduction have limited evidence (weak recommendation, low evidence).

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Endometriosis report** and aims to provide recommendations to aid in the management of Endometriosis. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Endometriosis. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

Section 5.0 References

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

II. Adult and Pediatric Quantity Limit?

This is either the adult or pediatric maximum amount of a drug that can be administered per day based on a maximum daily dose. If there is no clinical evidence

supporting the quantity limit for that relevant indication, this column will be left as Blank.

III. What information is available in the notes?

“Notes” section provides details of the prescribing edits, extra important drug information and special warning and precautions.

IV. Drug interactions

- A: No known interaction
- B: No action needed
- C: Monitor therapy
- D: Consider therapy modification
- X: Avoid combination

V. Defined Daily Dose

The Defined Daily Dose (DDD) is to be set based on the WHO recommendations https://www.whocc.no/ddd/definition_and_general_considera/

VI. REMS

A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.

Appendix B. Endometriosis Scope

Comparison of the 2020 and the 2023 Report

2020	Changes Performed	2023	Rationale
Section 1.0 Endometriosis Clinical Guidelines			

The European Society of Human Reproduction and Embryology (ESHRE) guideline: management of women with Endometriosis 2014	Updated	The European Society of Human Reproduction and Embryology (ESHRE) guideline: management of women with Endometriosis 2022 [4]	• Diagnostic process: laparoscopy was previously the gold standard. It is now recommended: "in patients with negative imaging results and/or where empirical treatment was unsuccessful or inappropriate".
			• To add treatment of Endometriosis-associated pain
			  ○ Analgesics
			  ○ Hormone Therapies
			  ▪ GnRH antagonists are additional (second-line) options
			  ▪ danazol and anti-progestogens are no longer recommended
			  ○ Surgery
			  ○ Adjunct medical therapies to surgery
			  ▪ Post-operative medical pain management may be offered to women who do not desire immediate pregnancy
			  ○ Assisted Reproductive Technology: extended GnRH agonist administration before ART is no longer recommended
			• Endometriosis Fertility index (EFI) was added to support decision-making in achieving pregnancy post-surgery.
			• New sections on pregnancy and fertility preservation, menopause, cancer, endometriosis in adolescents, and

			recurrence/secondary prevention
Not available	New Section	Clinical practice guidelines for Endometriosis in Japan (The 3rd edition) (2022) [6]	• To add treatment recommendations: symptomatic treatment and hormone therapy: • Symptomatic treatment: ○ NSAIDS ○ Chinese herbal medicine: Shakuyakukanzoto, tokishakuyakusan, keishibukuryogan, tokakujokito • Hormone therapy ○ Estrogen/ progestin (pseudopregnancy therapy) ○ Low-dose estrogen/ progestin combination (OC/LEP) ○ Progestins ▪ Dienogest ▪ Dydrogesterone ○ Danazol ○ GnRH agonists ○ GnRH antagonists: cetrorelix, ganirelix, relugolix ○ Levonorgestrel-releasing intrauterine system (LNG-IUS) ○ Aromatase inhibitors **Newly Introduced Medications**: (Not SFDA Registered) • Relugolix • Chinese herbal medicine: ○ Shakuyakukanzoto ○ Tokishakuyakusan ○ Keishibukuryogan ○ Tokakujokito **Newly Introduced SFDA Registered Medications:** • Cetrorelix

			• Ganirelix

Appendix C. MeSH Terms PubMed

The following is the result of the PubMed search conducted for hepatocellular carcinoma guideline search:

Query	Filters	Search Details	Results
(((Endometriosis[MeSH Terms]) OR (Endometrioses[Title/Abstract])) OR (Endometrioma[Title/Abstract])) OR (Endometriomas[Title/Abstract])	Guideline, in the last 5 years	("endometriosis"[MeSH Terms] OR "Endometrioses"[Title/Abstract] OR "Endometrioma"[Title/Abstract] OR "Endometriomas"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	9

Appendix D. Treatment Algorithm