EHC Guidelines

The diagnosis and management of endometriosis

EGYPTIAN HEALTH COUNCIL

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Abbreviations

- **GDG:** Guidelines Development Group
- **GPS:** Good Practice Statement.
- **GPS:** Good practice point
- **GRADE**: Grading of Recommendations Assessment, Development and Evaluation
- **GnRH** gonadotropin releasing hormone
- **LNG IUS** levonorgestrel intrauterine system
- **LUNA** laparoscopic uterosacral nerve ablation
- **NSAIDs** non-steroidal anti-inflammatory drugs
- **OCP** oral contraceptive pill

Glossary

A

Abdominal hysterectomy A hysterectomy carried out through a cut in the abdominal wall.

Add-back When taking certain hormones, Gonadotropin releasing hormone agonists (GnRH agonists), that put the body into an artificial menopause, the side effects can include menopausal symptoms such as hot flushes, loss of libido, vaginal dryness, headaches, loss of concentration or mood swings. A serious 'hidden' side effect can be loss of bone density – which can lead to osteoporosis. To try to counteract these side effects, small doses of oestrogen/progestogen in the form of HRT, Livial, or Norethisterone are given at the same time. They replace some of the hormones that are removed by the hormone treatments.

Adenomyosis A disease where endometrial tissue grows in the muscle layer of the wall of the womb, bleeding and causing pain. This is not the same as endometriosis.

Aromatase inhibitors Medication that stops (inhibits) the enzyme aromatase from working. Aromatase changes androgens into oestrogen. These drugs are occasionally being used to treat women with endometriosis, if those women have not responded to other treatments. These drugs are used to treat some breast cancers. They are still in the experimental phase for the treatment of endometriosis.

B

Bilateral salpingo-oophorectomy Surgery to removal both ovaries and fallopian tubes.

Bowel resection Surgery to remove a part of the bowel. The procedure may remove the portion of the bowel where an obstruction is located. Complications of a bowel resection include fistula, the formation of adhesions, and the possibility of a colostomy.

C

Cauterisation The removal or destruction of tissue with a laser or an electrical current. This can help with heavy bleeding and removal of endometriosis deposits.

Cervix The 'neck' of the womb or the opening between the body of the womb (uterus) and the vagina.

Chocolate cyst (endometrioma) A cyst in the ovary, filled with old blood, also known as an endometrioma. It occurs when there is bleeding into a cyst. They are called chocolate cysts because the blood is dark colored and looks like liquid chocolate.

Chronic: Persistent and lasting a long time.

D

Dysmenorrhea Painful periods.

Dyspareunia Painful sex.

E

Endometriosis is defined as a disease characterized by the presence of endometrium-like epithelium and/or stroma outside the endometrium and myometrium, usually with an associated inflammatory process

Endometrioma See chocolate cyst

F

Fallopian tube A tube that lies between the ovary and the womb, and transports the eggs to the womb. A woman has two Fallopian tubes.

Follicles Areas in the ovary, filled with fluid, containing the eggs that are released during ovulation.

G

Gonadotropins The hormones that control the function of your ovaries. They are called the Follicle Stimulating Hormone (FSH) and the Luteinizing Hormone (LH).

GnRH agonists and GnRH antagonists are both used to regulate hormone levels, but they work in different ways.

GnRH Agonists:

GnRH (Gonadotropin-releasing hormone) agonists mimic the natural GnRH that the body produces. When the medication is administered, it initially causes a surge of LH (luteinizing hormone) and FSH (follicle-stimulating hormone), which stimulates the ovaries to produce estrogen. Overtime GnRH agonists cause a decrease in LH and FSH production. This suppresses the ovaries and lowers estrogen levels.

GnRH Antagonists:

GnRH (Gonadotropin-releasing hormone) antagonists work differently. Instead of stimulating the release of LH (luteinizing hormone) and FSH (follicle-stimulating hormone), they block the GnRH receptors causing an immediate suppression of LH and FSH, stopping the ovaries from producing estrogen.

H

Hormone Replacement Therapy – HRT Medication used to mimic the effects of estrogen. It is prescribed after a hysterectomy or during menopause (either natural or medical) to

counteract the effects of the menopause. Those effects include hot flushes, night seat, loss of libido, mood swings, loss of bone density and vaginal dryness. HRT has its own risks and should be carefully considered before taking.

Hysterectomy The removal of the womb from the body during surgery. There are several different ways this is done, see below:

- **Total hysterectomy:** The removal of the womb (uterus) and the cervix, under anaesthetic.
- **Sub-total hysterectomy:** The removal of just the body of the womb (uterus).
- **Total hysterectomy with bilateral salpingo-oophorectomy:** Removal of the womb (uterus), cervix, ovaries and fallopian tubes.

Hysteroscopy A procedure in which the doctor examines the inside of the womb (uterus) under anaesthetic, by inserting an instrument (hysteroscope) into the womb. Minor surgery, such as the removal of a polyp, can be done at the same time.

I

In Vitro Fertilization (IVF) Literally means "in glass." Fertilization takes place outside the body in a small glass dish.

Infertility The inability to become pregnant; if a couple has a year of regular, unprotected sex and doesn't become pregnant, then that is also classed as infertility.

IUCD (Intrauterine Device) A device placed into the womb to prevent pregnancy.

L

Laparoscope: An instrument, like a small telescope with a light on one end, used to look at the inside of the pelvis, during a laparoscopy.

Luteal phase The part of the menstrual cycle between ovulation and menstruation.

Luteinising hormone (LH) One of the gonadotropins - the hormone that is responsible for releasing an egg.

Laparoscopy Usually done under general anaesthetic, a small telescope with a light on the end (the laparoscope) is inserted into the pelvis through the navel (belly button).

M

Menopause When a woman's ovaries stop functioning and her periods stop. This can either be artificially induced through drugs or a hysterectomy, or happen naturally. **Menorrhagia** Heavy periods.

Menstruation The monthly cycle where the body prepares for pregnancy.

Miscarriage Spontaneous loss of a fetus from the womb.

N

Nausea Feeling sick or queasy and needing to vomit.

Neurectomy The removal of a nerve, can be done to help relieve pain.

Neuropathic pain Pain caused by damage to the nervous system, which affects its ability to perceive pain. This pain is usually chronic and lasts longer than the time taken for

damaged tissue to heal. It can be treated with pain modifiers such as anti-depressants or anti-convulsants.

NSAIDs such as Ibuprofen, Voltarol and Ponstan (mefanemic acid) block the production of prostaglandins in the body. Prostaglandins occur naturally, in response to injury or disease, and cause pain and inflammation. They have a number of functions including making the womb contract during a period (which helps with the shedding of the womb lining). These contractions can cause pain. It is thought that women with endometriosis may produce more prostaglandins than women without the condition.

O

Oligomenorrhea Infrequent periods

Ongoing pregnancy A viable intrauterine pregnancy of at least 12 weeks duration confirmed on an ultrasound scan.

Oophorectomy The removal of one or both of the ovaries.

Ovarian cyst A growth in or on the ovary, filled with fluid. Called an endometrioma, when caused by endometriosis and filled with dark, old blood.

Ovarian Hyperstimulation Syndrome A side effect of fertility treatments that stimulate the ovaries to produce follicles (eggs). It can be life threatening. It occurs when too many follicles (with eggs) are produced.

Ovarian failure When the ovary no longer responds to the hormone FSH and does not produce follicles (with eggs) – either because it is damaged or hasn't formed properly or has no eggs left. This can be spotted by a blood test in which the FSH in the blood is raised.
Ovulate/ovulation When the egg is ripe and is released from the ovary. The follicle surrounding it breaks open and it will travel into the fallopian tube, to wait for fertilization. If the egg then becomes fertilized it will travel into the womb and implant.

P

Peritoneum The thin tissue that covers the walls of the pelvis and abdomen on the inside, as well as the pelvic organs.

Pregnancy When a baby develops inside the womb, from being an embryo to developing into a fetus. Pregnancy lasts for nine months until the woman gives birth.

Premature menopause Menopause that occurs naturally before the age of 40. Also known as premature ovarian failure.

Premature ovarian failure A condition where the ovary runs out of eggs before the woman would normally go through a menopause.

Presacral neurectomy A procedure where the nerves behind the womb are cut – the aim for this to stop or reduce pain.

R

Retrograde menstruation When you have a period, some of the endometrium (womb lining) flows backwards, out through the fallopian tubes and into the abdomen. This tissue may then implant itself on organs in the pelvis and grows. It has been suggested that most women experience some form of retrograde menstruation, but their bodies are able to clear this tissue and it does not deposit on the organs. This theory does not explain why

endometriosis has developed in some women after hysterectomy, or why, in rare cases, endometriosis has been discovered in some men, when they have been exposed to estrogen through drug treatments.

S

Salpingectomy The removal of the fallopian tube during surgery.

Side effects Problems that occur when medication or a treatment goes beyond the desired effect or problems that occur as well as the desired effect of the treatment/medications

T

Transvaginal scan an ultrasound performed through the vagina, using a special vaginal transducer. Transvaginal scans give better resolution of the ovaries and fallopian tubes. The procedure is usually painless, noninvasive, and safe.

Tumor A mass of cells growing inside the body. They can be benign or cancerous.

U

Ultrasound An investigative procedure where the inside of the body is looked at (visualised) using high-frequency sound waves.

Uterosacral ligaments: The supports that hold the womb in place inside the body. This is a common place to find endometriosis.

Executive Summary

This guideline offers evidence-based recommendations on diagnosis and management of female pelvic endometriosis. The recommendations are intended to provide healthcare professionals with practical guidance on appropriate and timely diagnosis and choosing the best evidence-based treatment modality of female pelvic endometriosis. resulting in improving health outcomes for people with this potentially disabling condition.

List of Recommendations

Recommendation	Strength
Diagnosis of endometriosis	
Symptoms: Clinicians should consider the diagnosis of endometriosis in individuals presenting with the following cyclical and non-cyclical signs and symptoms: dysmenorrhea, deep dyspareunia, dysuria, dyschezia, painful rectal bleeding or haematuria, shoulder tip pain, catamenial pneumothorax, cyclical cough/haemoptysis/ chest pain, cyclical scar swelling and pain, fatigue, and infertility	**GPS**
Signs: Offer an abdominal and pelvic examination to people 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.	**GPS**
If rectal endometriosis is suspected, a rectal examination may also be proactively performed to confirm the status of the bowel wall.	**GPS**
Diagnostic imaging	
Women with suspected endometriosis, further diagnostic steps, including imaging, should be considered even if the clinical examination is normal	**Strong**
Clinicians are recommended to use imaging (US or MRI) in the diagnostic work-up for endometriosis, but they need to be aware that a negative finding does not exclude endometriosis, particularly superficial peritoneal disease	**Strong**
Offer a transvaginal ultrasound scan to all women with suspected endometriosis, even if pelvic or abdominal examination is normal, to: identify ovarian endometriomas and deep endometriosis	**Conditional**
If a transvaginal scan is declined or not appropriate, consider transabdominal ultrasound scan of the pelvis	**GPS**
Do not use pelvic MRI as the primary investigation to diagnose endometriosis in people with symptoms or signs suggestive of endometriosis.	**Conditional**
Consider pelvic MRI to assess the extent of deep endometriosis involving the bowel, bladder or ureter	**Conditional**
Laparoscopy: surgical diagnosis	
In patients with negative imaging results, or where empirical treatment (hormonal contraceptives or progestogens) was unsuccessful, consider	**GPS**

offering laparoscopy for the diagnosis and treatment of suspected endometriosis	
Laparoscopic identification of endometriotic lesions should be confirmed by histopathologic examination of the lesions. However, a negative histology does not entirely rule out the disease	**GPS**
The procedure should be performed by a trained laparoscopic surgeon, who should perform and document a systematic inspection of the pelvis and abdomen	**GPS**
Biomarker: Do not use serum CA125 to diagnose endometriosis.	**Strong**
Treatment of endometriosis associated pain	
Pain control in endometriosis	
For women with pain associated with endometriosis-, consider a short trial (for example, 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 secondary or tertiary care center.	**GPS**
Advise patients that there is no evidence for or against the use of anti-neuropathic medications for pain associated with endometriosis	**GPS**
Women 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. • any underlying health condition has deteriorated.	**Conditional**
Hormonal treatment for endometriosis	
It is recommended to offer women hormone treatment (combined hormonal contraceptives, progestogens, GnRH agonists or GnRH antagonists) as one of the options to reduce endometriosis-associated pain	**Strong**
The GDG recommends that clinicians take a shared decision-making approach and take individual preferences, side effects, individual efficacy, costs, and availability into consideration when choosing hormone treatments for endometriosis-associated pain	**GPS**
When appropriate a levonorgestrel-releasing intrauterine system or an etonogestrel-releasing subdermal implant to reduce endometriosis-associated pain can be used	**Strong**
It is recommended to prescribe women GnRH agonists to reduce endometriosis-associated pain, although evidence is limited regarding dosage or duration of treatment	**Strong**
The GDG recommends that GnRH agonists are prescribed as second line (for example if hormonal contraceptives or progestogens have been ineffective) due to their side-effect profile	**GPS**
Clinicians should consider prescribing combined hormonal add-back therapy alongside GnRH agonist therapy to prevent bone loss and hypoestrogenic symptoms	**Strong**
In women with endometriosis-associated pain refractory to other medical or surgical treatment, it is recommended to prescribe aromatase inhibitors, as they reduce endometriosis-associated pain. Aromatase inhibitors may be	**Strong**

prescribed in combination with oral contraceptives, progestogens, GnRH agonists or GnRH antagonists	
Surgical management for endometriosis	
Laparoscopic management should be done by an expert in laparoscopic surgery	**GPS**
When surgery is performed, clinicians may consider excision instead of ablation of endometriosis to reduce endometriosis-associated pain	**Conditional**
It can be concluded that LUNA is not beneficial as an additional procedure to conventional laparoscopic surgery for endometriosis, PSN is beneficial for treatment of endometriosis-associated midline pain as an adjunct to conventional laparoscopic surgery	**GPS**
When performing surgery in women with ovarian endometrioma, clinicians should perform cystectomy instead of drainage and coagulation,	**Strong**
When performing surgery for ovarian endometrioma, specific caution should be used to minimize ovarian damage	**Strong**
Clinicians can consider performing surgical removal of deep endometriosis, as it may reduce endometriosis-associated pain and improves quality of life	**Conditional**
The GDG recommends that patients undergoing surgery particularly for deep endometriosis are informed on potential risks, benefits, and long-term effect on quality of life	**GPS**
Due to the heterogeneity of patient population, presentation, surgical approaches and techniques, it is difficult to make definitive recommendations on the specific techniques to be applied for the treatment of pain associated with deep endometriosis	**GPS**
In case of bowel endometriosis, a conservative approach should be chosen whenever possible.	**GPS**
Hysterectomy for endometriosis associated pain	
Clinicians can consider hysterectomy (with or without removal of the ovaries) with removal of all visible endometriosis lesions, in those women who no longer wish to conceive and failed to respond to more conservative treatments.	**Conditional**
The GDG recommends that when hysterectomy is performed, a total hysterectomy is preferred	**GPS**
When a decision is made whether to remove the ovaries, the long-term consequences of early menopause and possible need for hormone replacement therapy should be considered	**GPS**
Studies should evaluate factors that can be assessed prior to surgery and can predict a clinically meaningful improvement of pain symptoms. Such prognostic markers can be used to select patients that may benefit from endometriosis surgery	**GPS**
Women may be offered postoperative hormone treatment to improve the immediate outcome of surgery for pain in women with endometriosis if not desiring immediate pregnancy	**Conditional**
Non-medical interventions in endometriosis	
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	**GPS**

of life measures in women with endometriosis, as the potential benefits and harms are unclear.	
Treatment of endometriosis associated infertility	
Ovarian suppression	
In infertile women with endometriosis, clinicians should not prescribe ovarian suppression treatment to improve fertility.	**Strong**
Women seeking pregnancy should not be prescribed postoperative hormone suppression with the sole purpose to enhance future pregnancy rates.	**strong**
Those women who cannot attempt to or decide not to conceive immediately after surgery may be offered hormone therapy as it does not negatively impact their fertility and improves the immediate outcome of surgery for pain	**Conditional**
In infertile women with endometriosis, clinicians should not prescribe pentoxifylline, other anti-inflammatory drugs or letrozole outside ovulation-induction to improve natural pregnancy rates.	**Strong**
Surgical treatment	
The GDG recommends that the decision to perform surgery should be guided by the presence or absence of pain symptoms, patient age and preferences, history of previous surgery, presence of other infertility factors, ovarian reserve, and estimated Endometriosis Fertility Index (EFI).	**GPS**
Operative laparoscopy could be offered as a treatment option for endometriosis-associated infertility in rASRM stage I/II endometriosis as it improves the rate of ongoing pregnancy.	**Conditional**
Clinicians may consider operative laparoscopy for the treatment of endometrioma-associated infertility as it may increase their chance of natural pregnancy, although no data from comparative studies exist.	**Conditional**
Although no compelling evidence exists that operative laparoscopy for deep endometriosis improves fertility, operative laparoscopy may represent a treatment option in symptomatic patients wishing to conceive.	**Conditional**
Assessing the need for assisted reproduction after surgery	
Women should be counselled of their chances of becoming pregnant after surgery. To identify patients that may benefit from ART after surgery, the Endometriosis Fertility Index (EFI) should be used as it is validated, reproducible and cost-effective. The results of other fertility investigations such as their partner's sperm analysis should be taken into account.	**GPS**
Medically assisted reproduction	
IUI with endometriosis	
In infertile women with rASRM stage I/II endometriosis, clinicians may perform intrauterine insemination (IUI) with ovarian stimulation, instead of expectant management or IUI alone, as it increases pregnancy rates.	**Conditional**
Although the value of IUI in infertile women with rASRM stage III/IV endometriosis with tubal patency is uncertain, the use of IUI with ovarian stimulation could be considered.	**Conditional**
ART in women with endometriosis	

ART can be performed for infertility associated with endometriosis, especially if tubal function is compromised, if there is male factor infertility, in case of low EFI and/or if other treatments have failed	**Conditional**
A specific protocol for ART in women with endometriosis 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	**Conditional**
Women with endometriosis can be reassured regarding the safety of ART since the recurrence rates are not increased compared to those women not undergoing ART.	**Conditional**
In women with endometrioma, clinicians may use antibiotic prophylaxis at the time of oocyte retrieval, although the risk of ovarian abscess formation following follicle aspiration is low.	**GPS**
Medical therapies as an adjunct to MAR	
The extended administration of GnRH agonist prior to ART treatment to improve live birth rate in infertile women with endometriosis is not recommended, as the benefit is uncertain.	**Strong**
There is insufficient evidence to recommend prolonged administration of the COC/progestogens as a pre-treatment to ART to increase live birth rates.	**Conditional**
Surgical therapies as an adjunct to MAR	
Clinicians are not recommended to routinely perform surgery prior to ART to improve live birth rates in women with rASRM stage I/II endometriosis, as the potential benefits are unclear.	**Strong**
Clinicians are not recommended to routinely perform surgery for ovarian endometrioma prior to ART to improve live birth rates, as the current evidence shows no benefit and surgery is likely to have a negative impact on ovarian reserve.	**Strong**
Surgery for endometrioma prior to ART can be considered to improve endometriosis-associated pain or accessibility of follicles.	**GPS**
The decision to offer surgical excision of deep endometriosis lesions prior to ART should be guided mainly by pain symptoms and patient preference as its effectiveness on reproductive outcome is uncertain due to lack of randomised studies	**Strong**
Non-medical management strategies for infertility	
No recommendation can be made to support any non-medical interventions (nutrition, Chinese medicine, electrotherapy, acupuncture, physiotherapy, exercise, and psychological interventions) to increase fertility in women with endometriosis. The potential benefits and harms are unclear.	**GPS**
Fertility Preservation	
In case of extensive ovarian endometriosis, clinicians should discuss the pros and cons of fertility preservation with women with endometriosis. The true benefit of fertility preservation in women with endometriosis remains unknown	**Strong**
Impact of endometriosis on pregnancy and pregnancy outcome	
Patients should not be advised to become pregnant with the sole purpose of treating endometriosis, as pregnancy does not always lead to improvement of symptoms or reduction of disease progression.	**strong**

Complications related directly to pre-existing endometriosis lesions are rare, but probably under-reported. Such complications may be related to their decidualization, adhesion formation/stretching and endometriosis-related chronic inflammation. Although rare, they may represent life-threatening situations that may require surgical management.	**GPS**
Clinicians should be aware that there may be an increased risk of first trimester miscarriage and ectopic pregnancy in women with endometriosis.	**Strong**
Clinicians should be aware of endometriosis-associated complications in pregnancy, although these are rare. As these findings are based on low/moderate quality studies, these results should be interpreted with caution and currently do not warrant increased antenatal monitoring or dissuade women from becoming pregnant.	**Strong**
Endometriosis recurrence	
Prevention of endometriosis recurrence When surgery is indicated in women with an endometrioma, clinicians should perform ovarian cystectomy, instead of drainage and electrocoagulation, for the secondary prevention of endometriosis-associated dysmenorrhea, dyspareunia, and non-menstrual pelvic pain. However, the risk of reduced ovarian reserve should be taken into account	**Strong**
Clinicians should consider prescribing the postoperative use of a levonorgestrel-releasing intrauterine system (52 mg LNG-IUS) or a combined hormonal contraceptive for at least 18–24 months for the secondary prevention of endometriosis-associated dysmenorrhea	**Strong**
After surgical management of ovarian endometrioma in women not immediately seeking conception, clinicians are recommended to offer long-term hormone treatment (e.g. combined hormonal contraceptives) for the secondary prevention of endometrioma and endometriosis-associated related symptom recurrence.	**Strong**
For the prevention of recurrence of deep endometriosis and associated symptoms, long-term administration of postoperative hormone treatment can be considered	**Conditional**
Long-term administration of progestogen may reduce the recurrence of ovarian endometriotic cysts.	**Conditional**
Treatment of recurrent endometriosis Any hormone treatment or surgery can be offered to treat recurring pain symptoms in women with endometriosis	**Conditional**
Adolescent Endometriosis	
Clinical symptoms: In adolescents, clinicians should take a careful history and consider the following symptoms as suggestive of the presence of endometriosis: -chronic or a-cyclical pelvic pain, particularly combined with nausea, dysmenorrhea, dyschezia, dysuria, dyspareunia -cyclical pelvic pain	**Strong**
Clinical examination In case of virgin written informed consent from the patient and her parents before rectal examination	**GPS**
The recommendations for clinical examination in adults can be applied.	**GPS**

Imaging In case of virgin written informed consent from the patient and her parents before rectal u/s	**GPS**
Pelvic imaging with ultrasonography, regardless of findings on pelvic examination, also should be considered during evaluation for secondary dysmenorrhea.	**GPS**
Transvaginal ultrasound is recommended to be used in adolescents in whom it is appropriate non virgin, as it is effective in diagnosing ovarian endometriosis.	**Strong**
If a transvaginal scan is not appropriate, MRI, trans abdominal, trans-perineal, or trans rectal scan may be considered.	**Conditional**
Laboratory parameters Serum biomarkers (e.g., CA-125) are not recommended for diagnosing or ruling out endometriosis in adolescents.	**Strong**
Diagnostic laparoscopy In adolescents with suspected endometriosis where imaging is negative and imperical medical treatments (with NSAIDs and/or hormonal contraceptives) have not been successful, diagnostic laparoscopy may be considered.	**Conditional**
The appearance of endometriosis may be different in an adolescent than in an adult woman. In adolescents, endometriotic lesions are typically clear or red and can be difficult to identify for gynecologists unfamiliar with endometriosis in adolescents.	**GPS**
If a laparoscopy is performed, clinicians may consider taking biopsies to confirm the diagnosis histologically, although negative histology does not entirely rule out the disease.	**Strong**
Medical treatment Nonsteroidal anti-inflammatory drugs should be the mainstay of pain relief for adolescents with endometriosis.	**GPS**
In adolescents with severe dysmenorrhea and/or endometriosis-associated pain, Clinicians should prescribe hormonal contraceptives or progestogens	**Strong**
In adolescents with laparoscopically confirmed endometriosis and associated pain in whom hormonal contraceptives or progestogen therapy failed, clinicians may consider prescribing GnRH agonists combined with add-back therapy for up to 1 year, as they are effective and safe.	**Conditional**
If GnRH agonist treatment is considered, it should be used only after careful consideration and discussion of potential side effects and potential long-term health risks with a practitioner in a secondary or tertiary care setting	**GPS**
Combined medical and surgical treatment. In adolescents with endometriosis, clinicians should consider postoperative hormone therapy, as this may suppress recurrence of symptoms	**Strong**
Menopause and Endometriosis	
Treatment of endometriosis in postmenopausal women	
Clinicians may consider surgical treatment for postmenopausal women presenting with signs of endometriosis and/or pain to enable histological confirmation of the diagnosis of endometriosis	**conditional**
Clinicians should acknowledge the uncertainty towards the risk of malignancy in postmenopausal women. If a pelvic mass is detected, the	**GPS**

work-up and treatment should be performed according to national oncology guidelines	
For postmenopausal women with endometriosis-associated pain, clinicians may consider aromatase inhibitors as a treatment option especially if surgery is not feasible.	**Conditional**
Menopausal symptoms in women with a history of endometriosis	
Clinicians may consider combined menopausal hormone therapy (MHT) for the treatment of postmenopausal symptoms in women (both after natural and surgical menopause) with a history of endometriosis	**Conditional**
Clinicians should avoid prescribing estrogen-only regimens for the treatment of vasomotor symptoms in postmenopausal women with a history of endometriosis, as these regimens may be associated with a higher risk of malignant transformation	**Strong**
Clinicians should continue to treat women with a history of endometriosis after surgical menopause with combined estrogen-progestogen at least up to the age of natural menopause.	**GPS**
Menopause-related major health concerns in women with endometriosis	
Clinicians should be aware that women with endometriosis who have undergone an early bilateral salpingo-oophorectomy as part of their treatment have an increased risk of diminished bone density, dementia, and cardiovascular disease. It is also important to note that women with endometriosis have an increased risk of cardiovascular disease, irrespective of whether they have had an early surgical menopause	**GPS**
Extra pelvic endometriosis	
Clinicians should be aware of symptoms of extra-pelvic thoracic endometriosis, such as cyclical shoulder pain, cyclical spontaneous pneumothorax, cyclical cough, or nodules which enlarge during menses.	**GPS**
It is advisable to discuss diagnosis and management of extra-pelvic & thoracic endometriosis in a multidisciplinary team in a center with sufficient expertise	**GPS**
For abdominal extra-pelvic endometriosis, surgical removal is the preferred treatment, when possible, to relieve symptoms. Hormone treatment may also be an option when surgery is not possible or acceptable	**Conditional**
Asymptomatic endometriosis	
Treatment Clinicians should inform and counsel women about any incidental finding of endometriosis	**GPS**
Clinicians should not routinely perform surgical excision/ablation for an incidental finding of asymptomatic endometriosis at the time of surgery	**Strong**
Clinicians should not prescribe medical treatment in women with incidental finding of endometriosis	**Strong**
Monitoring Routine ultrasound monitoring of asymptomatic endometriosis can be considered.	**Conditional**
Primary prevention of endometriosis	

Although there is no direct evidence of benefit in preventing endometriosis in the future, women can be advised of aiming for a healthy lifestyle and diet, with reduced alcohol intake and regular physical activity	**Conditional**
The usefulness of hormonal contraceptives for the primary prevention of endometriosis is uncertain	**Conditional**

Introduction

Endometriosis is a chronic inflammatory disease defined as the presence of endometrium-like tissue outside the uterus.[1] Establishment and growth of such endometriotic tissue is estrogen-dependent [2], thus it is mostly found in women of reproductive age although the clinical consequences of endometriosis and its management can last well into post-menopause. The exact prevalence of endometriosis is unknown, but estimates range from 2 to 10% within the general female population but up to 50% in infertile women.[3, 4] Thus, it is estimated that currently at least 190 million women and adolescent girls worldwide are affected by the disease during reproductive age although some women may suffer beyond menopause.[5, 6] Whilst not all women with endometriosis are symptomatic, endometriosis-associated pain and infertility are the clinical hallmarks of the disease affecting not only women with endometriosis, but also their partners and families. An impact of endometriosis, and particularly pain symptoms, has been shown on quality of life, but also on a range of activities and life domains including physical functioning, everyday activities and social life, education and work, sex, intimacy and intimate partnerships, and mental health and emotional wellbeing.[7] The same review also reported an impact of infertility and concerns about possible infertility on the patient and the relationship with their partner.[7] Finally, endometriosis has a bearing on society in general e.g. through direct and indirect healthcare costs which are comparable to other common diseases such as type 2 diabetes, rheumatoid arthritis, and Crohn's disease.[8] Despite all of this, there still exists a large diagnostic void between the onset of symptoms and a reliable diagnosis averaging between 8-12 years. Therapeutic options range from improving pain symptoms and fertility prospects by means of hormone suppression of endogenous estrogen levels, pro-apoptotic and anti-inflammatory effects on endometriotic tissue, surgical removal, or destruction of endometriotic lesions and division of adhesions to management of chronic pain syndromes

Whilst there still exists a great unmet clinical need for improving many aspects of the diagnosis of the disease and the treatment of endometriosis-associated symptoms, there is a slowly growing body of studies which found the basis for the use of evidence-based recommendations which are compiled here.

Scope and Purpose

The objectives of this guideline are:

- To provide provide optimal practice recommendations for the management of women with suspected and confirmed endometriosis.

- To optimize outcomes for patients who suffer endometriosis associated pain and/or infertility.

Recommendations are provided on diagnosis and treatment for both relief of painful symptoms and for infertility due to endometriosis. Specific recommendations are provided on management of patients in whom endometriosis is found incidentally (without pain or infertility), adolescents and menopausal women with endometriosis. Adenomyosis is defined as the presence of ectopic endometrial tissue (endometrial stroma and glands) within the myometrium. Adenomyosis is not considered a form or subtype of endometriosis and hence not covered in the current guideline.

Target Audience

This guideline targets; healthcare professionals working as Obstetricians & Gynecologists, nurses, physicians working at emergency units, policy makers, hospital managers, and other stakeholders to apply the best practice and afford the most appropriate tools for women suffering of endometriosis.

Methodology

A comprehensive search for guidelines was done to identify the most relevant ones to consider for adaptation. The inclusion/exclusion criteria that were followed in the search and retrieval of guidelines to be adapted are:

We select guidelines only if they are:

- Evidence-based guidelines
- National and/or international guidelines
- Guidelines published from 2016 to 2025
- Peer reviewed publications
- Guidelines written in English language

We Exclude guidelines that are:

- Written by a single author not on behalf of an organization as guideline to be valid and comprehensive ideally requires multidisciplinary input.
- Published without references as the panel needs to know whether a thorough literature review was conducted and whether the current evidence was used in the preparation of the recommendations.

The following characteristics of the retrieved guidelines were summarized in a table:

- Developing organization/authors
- Date of publication, posting, and release
- Country/language of publication
- Dates of the search used by the source guideline developers

All retrieved Guidelines were screened and appraised using AGREE II instrument (www.agreetrust.org) by at least three members. The panel decided on a cut-off point or ranked the guidelines (any guideline scoring above 50% on the rigor dimension was retained).

Guidelines used in the adaptation process: [9-13]

1. Harada T, Taniguchi F, Kitajima M, Kitawaki J, Koga K, Momoeda M, Mori T, Murakami T, Narahara H, Osuga Y, Yamaguchi K. Clinical practice guidelines for endometriosis in Japan (The 3rd edition). J Obstet Gynaecol Res. 2022 Dec;48(12):2993-3044.
2. ESHRE (2022). Becker CM, Bokor A, Heikinheimo O, Horne A, Jansen F, Kiesel L, King K, Kvaskoff M, Nap A, Petersen K, Saridogan E, Tomassetti C, van Hanegem N, Vulliemoz N, Vermeulen N; ESHRE Endometriosis Guideline Group. ESHRE guideline: endometriosis. Hum Reprod Open. 2022 Feb 26;2022(2):hoac009.
3. Australian clinical practice guideline for the diagnosis and management of endometriosis (2021). RANZCOG, Melbourne, Australia.

   https://ranzcog.edu.au/wp-content/uploads/2022/02/Endometriosis-clinical-practice-guideline.pdf
4. ACOG Committee Opinion No. 760: Dysmenorrhea and Endometriosis in the Adolescent. Obstet Gynecol. 2018 Dec;132(6):e249-e258.
5. National Guideline Alliance (UK). Endometriosis: diagnosis and management. London: National Institute for Health and Care Excellence (NICE); 2024 Nov

Evidence assessment

According to WHO Handbook for Guidelines, we used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to assess the quality of a body of evidence, develop and report recommendations. GRADE methods are used by WHO because these represent internationally agreed standards for making transparent recommendations. Detailed GRADE information is available on the following sites:

- GRADE working group: http://www.gradeworkingroup.org
- GRADE online training modules: http://cebgrade.mcmaster.ca/
- GRADE profile software: http://ims.cochrane.org/revman/gradepro

Table 1: Quality and Significance of the four levels of evidence in GRADE:

Quality	Definition	Implications
High	The guideline development group is very confident that the true effect lies close to that of the estimate of the effect	Further research is very unlikely to change confidence in the estimate of effect
Moderate	The guideline development group is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low	Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the true effect	Further research is very likely to have an important impact on confidence in the estimate of effect and is unlikely to change the estimate
Very low	The group has very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	Any estimate of effect is very uncertain

Table 2; Factors that determine How to upgrade or downgrade the quality of evidence

Downgrade in presence of	Upgrade in presence of

Study limitations – 1 Serious limitations – 2 Very serious limitations	**Dose-response gradient** + 1 Evidence of a dose-response gradient
Consistency – 1 Important inconsistency	**Direction of plausible bias** + 1 All plausible confounders would have reduced the effect
Directness – 1 Some uncertainty – 2 Major uncertainty	**Magnitude of the effect** + 1 Strong, no plausible confounders, consistent and direct evidence + 2 Very strong, no major threats to validity and direct evidence
Precision – 1 Imprecise data	
Reporting bias – 1 High probability of reporting bias	

The strength of recommendations

The strength of a recommendation communicates the importance of adherence to the recommendation.

Strong recommendations: The GDG found that the desirable effects of adherence to the recommendation outweigh the undesirable effects. This means that in most situations the recommendation can be adopted.

Conditional recommendations: This means that the GDG found that there is:

- Greater uncertainty about the strength of evidence, or
- The recommendation may account for a greater variety in patient values and preferences, or
- The resource use makes the intervention suitable for some, but not for other locations.

Conditional recommendations **are still the best available evidence to date and** it can be adopted if it meets the conditions mentioned with it.

Good Practice Statement: Statements based on opinion of respected authorities, e.g. the ESHRE, ACOG, and the guidelines development group.

Recommendations

1. Diagnosis of endometriosis

1.1 Symptoms:

1.1.1 Clinicians should consider the diagnosis of endometriosis in women presenting with the following cyclical and non-cyclical symptoms:

- Dysmenorrhea.
- Deep dyspareunia.
- Dysuria or hematuria.
- Dyschezia or painful rectal bleeding.
- Shoulder tip pain.
- Catamenial pneumothorax.
- Cyclical cough, hemoptysis, chest pain.
- Cyclical scar swelling and pain.
- Fatigue.
- Infertility *(GPS).*[10, 16-19]

Justification

Overall, evidence to predict endometriosis based on clinical symptoms alone is weak and incomplete. In women seeking help from general practitioners, the following symptoms were found to be risk factors for endometriosis: abdominopelvic pain, dysmenorrhea, heavy menstrual bleeding, infertility, dyspareunia and/or postcoital bleeding and/or a previous diagnosis of ovarian cyst, irritable bowel syndrome or pelvic inflammatory disease. Reporting multiple symptoms increases the chance of endometriosis. In specialist health care, severe dysmenorrhea was found to be predictive of a diagnosis of endometriosis in infertile women, but this was not found in all studies.

Thus, endometriosis should be considered a possible diagnosis in women presenting with such clinical symptoms as it may result in an earlier diagnosis of endometriosis and in an improved quality of life for the patients.

1.2 Signs:

1.2.1 Perform an abdominal and pelvic examination to 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,
- Visible vaginal endometriotic lesions *(GPS).*[11, 13]

1.2.2 If rectal endometriosis is suspected, a rectal examination is indicated to confirm the status of the bowel wall *(GPS).*[9]

Justification

During a clinical examination of the pelvis, signs suggestive of endometriosis may be found, including tenderness; tethering of pelvic organs that decrease mobility of the pelvic organs and tissues; palpable plaques, nodules or areas of thickening (commonly in the posterior compartment and along the uterosacral ligaments) that may indicate endometriosis; fixed enlarged or tender ovarian masses; and visible vaginal endometriosis lesions on speculum examination, most commonly in the vaginal fornices (posterior or anterior).

1.3 Diagnostic Imaging:

1.3.1 In women with suspected endometriosis, further diagnostic steps, including imaging, should be considered even if the clinical examination is normal *(low level of evidence, Strong recommendation).*[10, 20, 21]

1.3.2 Clinicians are recommended to use imaging (US or MRI) in the diagnostic work-up for endometriosis, but they need to be aware that a negative finding does not exclude endometriosis, particularly superficial peritoneal disease *(low level of evidence, strong recommendation)*.[10, 20, 22-26]

1.3.3 Offer a transvaginal ultrasound scan to all women with suspected endometriosis, even if pelvic or abdominal examination is normal, to identify ovarian endometriomas and deep endometriosis *(very low level of evidence, conditional recommendation)*.[13]

1.3.4 If a transvaginal scan is not appropriate, consider transabdominal ultrasound scan of the pelvis *(GPS)*.[13]

1.3.5 Do not use pelvic MRI as the primary investigation to diagnose endometriosis in people with symptoms or signs suggestive of endometriosis *(very low level of evidence, conditional recommendation).*[11]

1.3.6 Consider pelvic MRI to assess the extent of deep endometriosis involving the bowel, bladder or ureter *(very low level of evidence, conditional recommendation)*.[11]

Justification

Taking the available data into account, it is likely that particularly dedicated transvaginal ultrasound in experienced hands but also MRI can replace surgery are the gold standard for the diagnosis of ovarian endometriosis cysts and deep endometriosis in the pelvis. However, the non-invasive diagnosis of superficial disease remains a significant challenge and can currently not accurately diagnosed or ruled out by the available imaging modalities**.** Thus, if symptoms persist, further investigation should be considered. The accuracy of ultrasound for the diagnosis of endometriosis is affected by the techniques used, the thoroughness of the examination and the expertise of the person undertaking the scan.

Although the evidence showed that ultrasound and MRI were reliable tests for identifying site-specific endometriosis in a specialist setting, MRI could not be compared with ultrasound because a person with endometriosis would not initially be sent for an MRI scan. However, if the ultrasound was inconclusive or negative, but deep endometrioses involving the bowel, bladder or ureter was suspected, then the person might be referred for an MRI scan. The recommendations for MRI should not extend to earlier or more superficial disease because the evidence for MRI was limited to the detection of deep infiltrating endometriosis. There are also cost and access implications, because MRI is more expensive than ultrasound and may not be available in all areas.

1.4 Laparoscopy: surgical diagnosis:

1.4.1 In patients with negative imaging results, or where empirical treatment (hormonal contraceptives or progestogens) was unsuccessful, consider offering laparoscopy for the diagnosis and treatment of suspected endometriosis *(GPS)*.[1, 10, 27-30]

1.4.2 Laparoscopic identification of endometriotic lesions should be confirmed by histopathologic examination of the lesions. However, a negative histology does not entirely rule out the disease *(GPS)*.[10, 24]

1.4.3 The procedure should be performed by a trained laparoscopic surgeon, who should perform and document a systematic inspection of the pelvis and abdomen*(GPS)*.[11]

Justification

As established above, there exist copious diagnostic challenges for endometriosis in general, in particular for superficial pelvic disease due a variety of factors including the lack of clinically relevant biomarkers, lack of specific symptoms and the inability of current imaging techniques to reliably identify or rule out small lesions. There exists the widespread concept that laparoscopy is the accepted standard to diagnose abdominal endometriosis. However, laparoscopic surgery, albeit its widespread use, is expensive, invasive, and associated with morbidity and mortality. On the other hand, direct, photographic, and histological proof of lesions could potentially be an important psychological factor for women who have been suffering from the symptoms of an otherwise invisible disease creating a platform of acceptance for themselves and their environment. The benefits of laparoscopic surgery need to be weighed up against its risks.

Practically, a two-step approach should be sought which would include a transvaginal (where appropriate) ultrasound followed by empirical treatment (if the patient is not trying to conceive). Particularly in the primary care setting if endometriosis is suspected, imaging results are negative and the affected person is not acutely trying to conceive, symptomatic patients usually are offered hormonal treatment mostly in the form of the oral contraceptive pill or progestogens as a first-line treatment. If symptoms improve, endometriosis is presumed the main underlying condition, although other clinical causes can (co-)exist. This 'blinded' approach is widely known as empirical treatment.

Laparoscopies are sometimes performed with inadequate examination of the pelvis, resulting in false negative results. Laparoscopic diagnosis should involve a systematic examination of the pelvis carried out by a gynecologist with training and skills in laparoscopic surgery, because it is possible to miss significant endometriosis. When the findings from a systematic review of the pelvis are negative for endometriosis, or histological samples taken from the pelvis are negative for endometriosis, the person should be reassured that endometriosis is not the cause of their symptoms and should be offered appropriate treatment for persistent symptoms.

1.5 Biomarkers:

1.5.1 Do not use serum CA125 to diagnose endometriosis (*moderate level of evidence, Strong recommedation)*.[10, 11, 13]

Justification

Numerous biomarkers have been proposed; if these prove to be sufficiently accurate, a blood test could provide a relatively safe and cheap method of diagnosis that is readily

available in community settings. Serum CA125 is the most widely studied biomarker in populations with endometriosis, but the quality of evidence is very low and the rate of false negative test results is too high to promote its use in clinical practice at this time. A CA125 test does not add anything to the diagnostic strategy, apart from a possible delay and additional costs for further unnecessary referral and investigation.

2. Treatment of endometriosis associated pain

2.1 Pain control in endometriosis

2.1.1 For women with pain associated with endometriosis-, consider a short trial (for example, 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 (*GPS)*.[11]

Justification

The evidence for use of NSAIDs for management of pain symptoms related to endometriosis is scarce and limited to one small RCT. There is a general anti-inflammatory effect of some analgesics, they can be used in conjunction with surgery and/or hormonal treatments and they may possibly prevent of complications of chronic pain (e.g., peripheral, and central sensitization). However, analgesics may also have side effects, and NSAIDs specifically may have some gastrointestinal side effects. There is no evidence that analgesics have an effect on disease progression. Overall, with limited risks and considering the wide availability and use of analgesics, the GDG concluded that NSAIDs or other analgesics may be offered for the treatment of endometriosis-associated pain.

2.1.2 Advise patients that there is no evidence for or against the use of anti-neuropathic medications for pain associated with endometriosis (*GPS*).[11]

2.1.3 Women 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.
- any underlying health condition has deteriorated (*GPS).*[11]

2.2 Hormonal treatment for endometriosis

2.2.1 It is recommended to offer women hormone treatment (combined hormonal contraceptives, progestogens, GnRH agonists or GnRH antagonists) as one of the options to reduce endometriosis-associated pain *(moderate level of evidence, strong recommendation).*[31-35]

2.2.2 The GDG recommends that clinicians take a shared decision-making approach and take individual preferences, side effects, individual efficacy, costs, and availability into consideration when choosing hormone treatments for endometriosis-associated pain (*GPS)*. [31-35]

Justification

There is moderate quality evidence of benefit for all listed hormone treatments for relief of painful symptoms related to endometriosis. As there is no evidence that hormone

treatments have a negative effect on disease progression and they generally have limited side effects, prescribing hormone treatment is recommended. Moreover, hormone treatments, such as the contraceptive pill, may be indicated for contraception anyway. As there is no evidence of superiority of one hormone treatment compared to others, the GDG recommends a shared decision-making approach. These overarching recommendations should be read and applied in consideration of the remainder of this section which provides more detailed information on the different medical treatments including their efficacy and side-effect profile.

2.2.3 It is recommended to prescribe women a levonorgestrel-releasing intrauterine system or an etonogestrel-releasing subdermal implant to reduce endometriosis-associated pain *(moderate level of evidence, strong recommendation)*.[36-39]

Justification

There is sufficient evidence on the effectiveness of progestogens and anti-progestogens, including the levonorgestrel-releasing intrauterine system and the etonogestrel-releasing subdermal implant, to support their use in reducing pain in women with endometriosis (strong recommendation). The GDG stresses that clinicians should consider the side-effect profiles to tailor the medical treatment towards improving symptoms and quality of life. The GDG does not recommend danazol as a treatment for endometriosis-associated pain and considered it no longer relevant to include anti-progestogens in the recommendation.

With regards to the LNG-IUS, a review of five trials showed that the clinical efficacy was equivalent to that of GnRH agonist, but also that LNG-IUS may have some clinical advantages. LNG-IUS and ENG were shown to be equally effective in one study. A strong recommendation was formulated for both LNG-IUS and ENG as progestogen-treatment.

2.2.4 Clinicians should consider prescribing combined hormonal add-back therapy alongside GnRH agonist therapy to prevent bone loss and hypoestrogenic symptoms (*moderate level of evidence, strong recommendation).* [35-37, 40-42]

Justification

From the Cochrane review, it can be concluded that GnRH agonists are effective in the relief of endometriosis-associated pain (strong recommendation), but evidence is limited regarding dosage or duration of treatment. Based on the evidence to date, no specific GnRH agonist can be recommended over another in relieving endometriosis-associated pain. There is evidence of considerable side effects with GnRH agonists, which should be discussed with the patient when offering this treatment. There is moderate quality evidence, summarized in a systematic review,[35] that addition of add-back therapy when prescribing GnRH agonist treatment prevents bone loss, while it does not affect the efficacy of the GnRH agonist treatment. As such, add-back treatment is recommended (strong recommendation). Considering the possible impact on BMD, The GDG recommends that in young women and adolescents, GnRH agonist should be used after careful consideration and as second line of therapy and after discussion with a practitioner in a secondary or tertiary care setting, considering potential side effects and long-term health risks (e.g., bone health).

2.2.5 In women with endometriosis-associated pain refractory to other medical or surgical treatment, it is recommended to prescribe aromatase inhibitors, as they reduce endometriosis-associated pain. Aromatase inhibitors may be prescribed in combination with oral contraceptives, progestogens, GnRH agonists or GnRH antagonist *(low level of evidence, strong recommendation)*.[43, 44]

Justification

The evidence consists of a systematic review from 2011, including mostly non-randomized controlled studies and case reports in women with rectovaginal endometriosis or women that are refractory to previous surgical and medical treatment, and 2 more recent studies. Evidence on the long-term effects of aromatase inhibitors is lacking. Due to the severe side effects (vaginal dryness, hot flushes, diminished bone mineral density), aromatase inhibitors should only be prescribed to women after all other options for medical or surgical treatment are exhausted. Considering these aspects, aromatase inhibitors should be preserved for women with endometriosis-associated pain refractory to other medical or surgical treatment.

2.3 Surgical treatment for pain in endometriosis

2.3.1 Laparoscopic management should be done by an expert in laparoscopic surgery (*GPS*).

2.3.2 When surgery is performed, clinicians may consider excision instead of ablation of endometriosis to reduce endometriosis-associated pain *(low level of evidence, conditional recommendation)*.[45-48]

Justification

The evidence for ablation versus excision is based on studies that include women with heterogeneous forms of endometriosis. Some of these studies excluded women with deep endometriosis, in which ablation is not usually applied anyway. The excisional approach is likely to be more suitable for deep endometriosis lesions, as it is impossible to know if the entire lesion is destroyed with ablative techniques.

2.3.3 It can be concluded that LUNA is not beneficial as an additional procedure to conventional laparoscopic surgery for endometriosis, as it offers no additional benefit over surgery alone. Presacral Neurectomy (PSN) is beneficial for treatment of endometriosis-associated midline pain as an adjunct to conventional laparoscopic surgery, but it should be stressed that PSN requires a high degree of skill and is associated with an increased risk of adverse effects such as intraoperative bleeding, and postoperative constipation, urinary urgency and painless first stage of labor (GPS).[49-53]

2.3.4 When performing surgery in women with ovarian endometrioma, clinicians should perform cystectomy instead of drainage and coagulation, as cystectomy reduces recurrence of endometrioma and endometriosis-associated pain *(low level of evidence, strong recommendation)*.[54-60]

2.3.5 When performing surgery for ovarian endometrioma, specific caution should be used to minimize ovarian damage *(very ow level of evidence, strong recommendation)*. [54-60]

Justification

Cystectomy is probably superior to drainage and coagulation in women with ovarian endometrioma (≥ 3cm) regarding the recurrence of endometriosis-associated pain and the

recurrence of endometrioma (Hart, et al., 2008), which supports the formulation of a strong recommendation. Longer follow-up data show similar recurrence rates for cystectomy and CO2 laser vaporization. Whilst superiority of excision over drainage and coagulation/ablation can be expected, possible difficulties in removal of very small endometriomas should be kept in mind due to lack of a clear surgical plane. With regards to ovarian reserve, data show that ovarian surgery may have an impact on ovarian reserve, but the data comparing the impact of different techniques should be interpreted with caution. When contemplating surgery for endometriomas, particularly for recurrent endometriomas, ovarian reserve and ovarian damage should be carefully considered. For the comparison of cystectomy and CO2 laser vaporization, one RCT and one retrospective study were available [56, 61], both concluding that there are similar recurrence rates beyond the first year for the treatment of endometriomas both techniques, Carmona et al. also reported that the recurrence rates may be lower after cystectomy in the first year. In the included studies, patients were included with endometriomas and endometriosis-associated symptoms (pain and/or infertility). The guideline group would like to clarify that in women with a diagnosed endometrioma and pain symptoms, other forms of endometriosis including deep endometriosis is commonly detected during surgery. Although not discussed, nor considered in most of the studies, this needs to be considered in clinical practice.

2.3.6 Clinicians can consider performing surgical removal of deep endometriosis, as it may reduce endometriosis-associated pain and improves quality of life (*low level of evidence, conditional recommendation)*.[62-65]

2.3.7 The GDG recommends that patients undergoing surgery particularly for deep endometriosis are informed on potential risks, benefits, and long-term effect on quality of life (*GPS*). [62-65]

2.3.8 Due to the heterogeneity of patient population, presentation, surgical approaches and techniques, it is difficult to make definitive recommendations on the specific techniques to be applied for the treatment of pain associated with deep endometriosis (*GPS)* [62-65]

Justification

Overall, data show that surgery improves pain and quality of life in women with deep endometriosis. Still, the literature regarding treatment and outcome of deep endometriosis surgery should be interpreted with caution. It is of paramount importance that type of study, surgical approach, surgical technique, and the way outcome is measured is taken into account. There is a lack of consistency in the way the studies reported outcome, and the systematic review on this topic was based on small studies and case reports. These limitations are reflected in the evidence level. As surgery in women with deep endometriosis is possibly associated with significant intraoperative and postoperative complication rates, the recommendation was formulated as a conditional recommendation and complemented with a GPS suggestion that such surgery is ideally performed in a center of expertise, and only after the patient is informed on potential risks, benefits, and long-term effects.

2.3.9 In case of bowel endometriosis, a conservative approach should be chosen whenever possible It is concluded that a conservative approach should be chosen whenever possible. Radical resection of all endometriosis nodules does not mean that a conservative attitude towards surgical technique/options could not be maintained. A least traumatic, but radical resection with a more tailored/patient-centered approach with perioperative decision-making is preferred (GPS).[63, 66]

2.3.10 Clinicians can consider hysterectomy (with or without removal of the ovaries) with removal of all visible endometriosis lesions, in those women who no longer wish to conceive and failed to respond to more conservative treatments. This may be a particularly good option in women with significant concomitant adenomyosis. Women should be informed that hysterectomy will not necessarily cure the symptoms or the disease (*low level of evidence, Conditional recommendation)*.[67, 68]

2.3.11 When a decision is made whether to remove the ovaries, the long-term consequences of early menopause and possible need for hormone replacement therapy should be considered (*GPS*). [67, 68]

2.3.12 The GDG recommends that when hysterectomy is performed, a total hysterectomy is preferred. This recommendation is based on possible risk of persistent endometriosis and adenomyosis within the retained cervix and/or adjacent to it (*GPS).* [67, 68]

Justification

Hysterectomy for endometriosis-associated pain seems to be effective for relieving symptoms and significantly reduces the need for re-operation. This may be a particularly good option in women with significant concomitant adenomyosis. It should be considered that hysterectomy, especially when combined with bilateral salpingo-oophorectomy, is not an option for women still wishing to conceive. Additionally, hysterectomy with bilateral salpingo-oophorectomy may have a significant long-term impact and may create a need for hormone replacement therapy. The GDG stresses that women with endometriosis may still experience pain symptoms after hysterectomy, due to residual endometriosis or centralization of pain. The GDG recommends that when hysterectomy is performed, a total hysterectomy (i.e., removal of uterus and cervix) is preferred. This recommendation is based on possible risk of persistent endometriosis and adenomyosis within the retained cervix and/or adjacent to it with subtotal hysterectomy

2.3.13 Studies should evaluate factors that can be assessed prior to surgery and can predict a clinically meaningful improvement of pain symptoms. Such prognostic markers can be used to select patients that may benefit from endometriosis surgery (*GPS*).[66, 69, 70]

Justification

The guideline group confirms the recommendation from the previous ESHRE guideline. Considering this (strong) recommendation, the GDG acknowledges that in clinical practice, surgeons prescribe preoperative medical treatment with GnRH agonists as this can facilitate surgery due to reduced inflammation, vascularization of endometriosis lesions and adhesions. However, there are no controlled studies supporting this. From a patient perspective, medical treatment should be offered before surgery to women with painful symptoms in the waiting period before the surgery can be performed, with the purpose of reducing pain before, not after, surgery.

2.3.14 Women may be offered postoperative hormone treatment to improve the immediate outcome of surgery for pain in women with endometriosis if not desiring immediate pregnancy (*low level of evidence, conditional recommendation*).[71-75]

Justification

Based on the current evidence from the Cochrane review by Chen et al., the GDG concluded that there is only a very moderate benefit of postoperative hormone therapy (within 6 months after surgery) if this treatment is prescribed with the sole aim of improving the outcome of surgery. Furthermore, there is inconsistency between the studies on whether postoperative hormone treatment has a favorable effect on pain recurrence or disease recurrence after surgery. With no proven harm, postoperative hormone therapy may be prescribed for other indications, such as contraception or secondary prevention.

2.4 Non-medical interventions in endometriosis

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 in women with endometriosis, as the potential benefits and harms are unclear.

Adequately designed trials are needed to define the potential benefits of non-medical interventions (nutrition, Chinese medicine, electrotherapy, acupuncture, physiotherapy, exercise, and psychological interventions) in endometriosis. Further research into such interventions for women with endometriosis that employ evidence-based protocols with high intervention integrity is recommended (*GPS).*[76-80]

3. Treatment of endometriosis associated infertility

3.1 Ovarian suppression

3.1.1 In infertile women with endometriosis, clinicians should not prescribe ovarian suppression treatment to improve fertility (*low level of evidence, strong recommendation*).[10, 81]

3.1.2 Women seeking pregnancy should not be prescribed postoperative hormone suppression with the sole purpose to enhance future pregnancy rates (*low level of evidence, strong recommendation)*.

3.1.3 Those women who cannot attempt to or decide not to conceive immediately after surgery may be offered hormone therapy as it does not negatively impact their fertility and improves the immediate outcome of surgery for pain (*low level of evidence, conditional recommendation*).[10, 71, 82]

3.1.4 In infertile women with endometriosis, clinicians should not prescribe pentoxifylline, other anti-inflammatory drugs or letrozole outside ovulation-induction to improve natural pregnancy rates (*very low level of evidence, strong recommendation*).[10, 83, 84]

Justification

Based on the results of the Cochrane review, suppression of ovarian function (by means of danazol, GnRH agonists, progestogens, OCP) to improve fertility in women with endometriosis is not effective and should not be offered for this indication alone (strong recommendation).

It should be noted that several patients included in the Hughes *et al.* review had undergone surgical treatment before randomization for ovarian suppression or no treatment. This observation complicates any recommendations regarding ovarian suppression and post-surgical ovarian suppression, discussed in the following section.

Studies show no benefit of pentoxifylline, postoperative aromatase inhibitor (letrozole), or postoperative GnRH agonist (triptorelin) to improve pregnancy rates in women with endometriosis. Therefore, the intervention is not recommended (strong recommendation).

The GDG considered that ovarian suppression after surgical treatment for endometriosis should not be prescribed to improve pregnancy rates (strong recommendation). The GDG also considered that ovarian suppression after surgical treatment does probably not have a negative effect on the chances of pregnancy, and therefore, it may be prescribed for pain management, or in women that cannot attempt to conceive immediately after surgery, but not with the sole aim of improving pregnancy rates (conditional recommendation). This is consistent with the earlier recommendation "Women may be offered postoperative hormone treatment to improve the immediate outcome of surgery for pain in women with endometriosis."

3.2 Surgical treatment

3.2.1 The GDG recommends that the decision to perform surgery should be guided by the presence or absence of pain symptoms, patient age and preferences, history of previous surgery, presence of other infertility factors, ovarian reserve, and estimated EFI *(GPS).*

3.2.2 Regarding peritoneal endometriosis Although laparoscopic surgery was found to increase (natural) viable intrauterine pregnancy rates, no data were found on live birth rates. Operative laparoscopy could be offered as a treatment option for endometriosis associated infertility in rASRM stage I/II endometriosis as it improves the rate of ongoing pregnancy (*low level of evidence, conditional recommendation)* [10, 27, 56, 85]

3.2.3 Regarding ovarian endometriosis Clinicians may consider operative laparoscopy for the treatment of endometrioma associated infertility as it may increase their chance of natural pregnancy, although no data from comparative studies exist *(very low level of evidence, conditional recommendation*).[10, 86]

3.2.4 Regarding deep endometriosis Although no compelling evidence exists that operative laparoscopy for DE improves fertility, operative laparoscopy may represent a treatment option in symptomatic patients wishing to conceive *(very low level of evidence, conditional recommendation).*[10, 87]

Justification

In the review of Bafort *et al.*, surgery in women with rASRM stage I/II endometriosis improved the rate of ongoing pregnancy. The GDG formulated a conditional recommendation to offer operative laparoscopy. However, the GDG also acknowledges that data on live birth rates and direct comparison with medically assisted reproduction are lacking

Similar considerations were made for endometrioma and deep endometriosis surgery; with a lack of comparative studies evaluating spontaneous conception after surgery compared to no surgery, no strong recommendations could be formulated. The GDG added clarification that the decision to perform surgery should be guided by other factors.

3.3 Assessing the need for assisted reproduction after surgery

3.3.1 Women should be counselled of their chances of becoming pregnant after surgery. To identify patients that may benefit from ART after surgery, the Endometriosis Fertility Index (EFI) should be used as it is validated, reproducible and cost-effective. The results of other fertility investigations such as their partner's sperm analysis should be taken into account (*GPS*) [10, 88]

Justification

It is suggested that the EFI is used for better patient phenotyping in studies on surgical treatment and/or the place of medically assisted reproduction (MAR) in endometriosis-related infertility. The role of the EFI as a pre-surgical triage tool should be validated.

3.4 Medically assisted reproduction

3.4.1 Intrauterine insemination in women with endometriosis

3.4.1.1 In infertile women with rASRM stage I/II endometriosis, clinicians may perform intrauterine insemination (IUI) with ovarian stimulation, instead of expectant management or IUI alone, as it increases pregnancy rates *(very low level of evidence, conditional recommendation).* [10, 89-92]

3.4.1.2 Although the value of IUI in infertile women with rASRM stage III/IV endometriosis with tubal patency is uncertain, the use of IUI with ovarian stimulation could be considered (*very low level of evidence, conditional recommendation).*[10, 89-92]

Justification

In women with AFS/ASRM stage I/II endometriosis, IUI with ovarian stimulation may be effective in increasing live birth rate, compared with expectant management and effective in increasing biochemical pregnancy rate, compared to IUI alone (conditional recommendation). In these women, clinicians may consider performing intrauterine insemination with ovarian stimulation within 6 months after surgical treatment, since pregnancy rates are similar to those achieved in unexplained infertility.[90]

3.4.2 Assisted reproductive technology in women with endometriosis.

3.4.2.1 ART can be performed for infertility associated with endometriosis, especially if tubal function is compromised, if there is male factor infertility, in case of low EFI and/or if other treatments have failed (*low level of evidence, Conditional recommendation*).[10, 93-97]

3.4.2.2 A specific protocol for ART in women with endometriosis 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 (*very low level of evidence, conditional recommendation).*[10, 98-101]

3.4.2.3 Women with endometriosis can be reassured regarding the safety of ART since the recurrence rates are not increased compared to those women not undergoing ART *(moderate level of evidence, conditional recommendation).*[10, 102]

3.4.2.4 In women with endometrioma, clinicians may use antibiotic prophylaxis at the time of oocyte retrieval, although the risk of ovarian abscess formation following follicle aspiration is low *(GPS).*[10, 103]

Justification

Overall, in infertile women, most of the evidence does not demonstrate a negative impact of endometriosis (compared to non-endometriosis patients) on live birth rate after ART, even if the ovarian response and clinical pregnancy rates are lower. Therefore, ART may be effective for endometriosis-associated endometriosis, and is recommended (conditional recommendation) in women with other infertility factors. The severity of the disease might play a role with stage III-IV endometriosis potentially decreasing the live birth rate. The available evidence failed to demonstrate that a specific ART protocol should be favored in patients with endometriosis.

From a systematic review including moderate quality evidence, ART was not associated with increased endometriosis recurrence rate. A conditional recommendation was formulated to inform and/or reassure patients. The use of antibiotic prophylaxis at the time of oocyte retrieval in women with endometriomas seems reasonable and is recommended as a good practice point. There is no evidence on whether IUI or ART is superior in women with endometriosis.

3.4.3 Medical therapies as an adjunct to MAR

3.4.3.1 The extended administration of GnRH agonist prior to ART treatment to improve live birth rate in infertile women with endometriosis is not recommended, as the benefit is uncertain (*very low level of evidence, strong recommendation).*[10, 104-106]

3.4.3.2 There is insufficient evidence to recommend prolonged administration of the COC/progestogens as a pre-treatment to ART to increase live birth rates (*very low level of evidence, conditional recommendation)*.[10, 104-106]

Justification

Based on the Cochrane review [104], with the limitations as mentioned above, the merit of 3–6 months GnRH agonist administration to women with endometriosis prior to ART compared to no pre-treatment is uncertain and requires further high-quality trials to determine its impact With uncertain benefit, the administration of GnRH agonist prior to ART treatment cannot be recommended.

The data concerning the use of OCP or progestogens as a pre-treatment before ART for improving ART outcomes are very limited and do not allow to draw any conclusion. This does not preclude use of OCP for planning purposes.

3.4.4 Surgical therapies as an adjunct to MAR

3.4.4.1 Clinicians are not recommended to routinely perform surgery prior to ART to improve live birth rates in women with rASRM stage I/II endometriosis, as the potential benefits are unclear (*low level of evidence, strong recommendation*).[10, 93, 107, 108]

3.4.4.2 Clinicians are not recommended to routinely perform surgery for ovarian endometrioma prior to ART to improve live birth rates, as the current evidence shows no benefit and surgery is likely to have a negative impact on ovarian reserve (*low level of evidence, strong recommendation*).[10, 93, 107, 108]

3.4.4.3 Surgery for endometrioma prior to ART can be considered to improve endometriosis associated pain or accessibility of follicles (*GPS*).[10, 93, 107, 108]

3.4.4.4 The decision to offer surgical excision of deep endometriosis lesions prior to ART should be guided mainly by pain symptoms and patient preference as its effectiveness on reproductive outcome is uncertain due to lack of randomised studies (*very low level of evidence*, *strong recommendation*).[10, 93, 109]

Justification

The evidence regarding surgery prior to treatment with ART in women with stage I/II endometriosis is of low quality and based on a single retrospective study. Although this study suggests that surgery may have a beneficial effect on ART outcomes, the GDG considered more data are needed to confirm the benefit of surgery for peritoneal disease for improving ART outcomes, and to be able to recommended it in routine practice. A strong recommendation stating that laparoscopy should not be routinely performed prior to ART with the aim of improving ART outcomes was formulated.

Based on two systematic reviews and meta-analyses, surgical removal of endometrioma before ART does not appear to improve the live birth rate while it is likely reducing ovarian reserve. As such, a strong recommendation was formulated against surgery with the sole aim to improve ART outcomes. Additionally, a good practice point was formulated stating that surgery can be performed for other indications.

When surgical resection of endometrioma prior to ART is necessary, no specific techniques can be recommended. Ovarian cystectomy has the potential of reducing the risk of recurrence.

From the literature, there is no evidence from randomized controlled trials to recommend performing surgical excision of deep nodular endometriotic lesions prior to ART to improve reproductive outcomes. However, these women often suffer from pain, requiring surgical treatment. The GDG strongly recommends basing a decision to perform surgery on pain symptoms and patient preferences. In symptomatic infertile women with previous failed ART and deep endometriosis, surgical removal of the lesions may be (re)considered.

3.4.5 Non-medical treatment strategies

3.4.5.1 No recommendation can be made to support any non-medical interventions (nutrition, Chinese medicine, electrotherapy, acupuncture, physiotherapy, exercise, and psychological interventions) to increase fertility in women with endometriosis. The potential benefits and harms are unclear (*GPS*).[10, 110, 111]

Justification

Only small studies of low quality could be identified investigating surgery and medication and/or CM to improve subfertility. Though there is a lack of research specifically addressing the impact of non-medical strategies in the treatment of endometriosis-related symptoms, more studies are emerging. It seems evident that patients are searching for alternative ways of managing and coping without or alongside surgical and pharmacological interventions.

3.4.6 Fertility preservation

3.4.6.1 In case of extensive ovarian endometriosis, clinicians should discuss the pros and cons of fertility preservation with women with endometriosis. The true benefit of fertility preservation in women with endometriosis remains unknown *(very low level of evidence, strong recommendation).* [10, 112-116]

Justification

Oocyte cryopreservation is expensive and exposes women to some clinical risks. Although the study of Cobo *et al.* shows the feasibility of fertility preservation (oocyte freezing) in women with ovarian endometriosis, still many questions (e.g. (cost) effectiveness) remain unanswered, and there is currently insufficient data to support fertility preservation for all women with endometriosis. It is acknowledged that for some women with endometriosis, fertility preservation may increase their future chances of pregnancy, but there is no evidence on criteria to select those women. Based on these considerations, the GDG formulated a strong recommendation for counselling and information provision.

3.4.7 Impact of endometriosis on pregnancy and pregnancy outcome

3.4.7.1 Effect of pregnancy on endometriotic lesions

- Patients should not be advised to become pregnant with the sole purpose of treating endometriosis, as pregnancy does not always lead to improvement of symptoms or reduction of disease progression (*very low level of evidence, strong recommendation*).[10, 117, 118]

- Endometriomas may change in appearance during pregnancy. In case of finding an atypical endometrioma during ultrasound in pregnancy, it is recommended to refer the patient to a center with appropriate expertise (*very low level of evidence, strong recommendation*).[10, 117, 118]

Justification

Although this is considered as a narrative question, recommendations were formulated on safety aspects. The first strong recommendation is based on the evidence summarized in high quality systematic reviews, showing a variable impact of pregnancy on endometriotic lesions. Patients are being advised to become pregnant to cure their endometriosis, and the data clearly indicate that this advice is incorrect. The GDG therefore considered it relevant and important to recommend that women with endometriosis should not be advised to become pregnant with the sole purpose of treating endometriosis.

For the second (strong) recommendation, there are data showing that endometrioma may change appearance during pregnancy, but that this is often unknown and not recognized. As this may lead to surgical intervention and termination of pregnancy, the GDG formulated a recommendation for referral to a center with expertise

3.4.7.2 Possible complications during pregnancy from a pre-existing endometriosis lesion

- Complications related directly to pre-existing endometriosis lesions are rare, but probably under reported. Such complications may be related to their decidualization, adhesion formation/stretching and endometriosis-related chronic inflammation (endometrioma rupture or infection, gastrointestinal manifestation even bowel spontaneous perforation, urinary manifestations and even case recorded uterine rupture). Although rare, they may represent life-threatening situations that may require surgical management (*GPS*).[10, 117, 118]

3.4.7.3 Impact of endometriosis on early pregnancy (1st trimester)

- Clinicians should be aware that there may be an increased risk of first trimester miscarriage and ectopic pregnancy in women with endometriosis (*low level of evidence, strong recommendation*).[10, 117, 118]

Justification

Both miscarriage rate and ectopic pregnancy rate are increased in women with endometriosis versus controls, although this is based on low/moderate quality data. Therefore, higher vigilance is required in case of symptoms suggestive of miscarriage or ectopic pregnancy, such as vaginal bleeding and abdominal pain in the first trimester of pregnancy.

3.4.7.4 Impact of endometriosis on 2nd and 3rd trimester pregnancy and neonatal outcome

- Clinicians should be aware of endometriosis-associated complications in pregnancy, although these are rare. As these findings are based on low/moderate quality studies, these results should be interpreted with caution and currently do not warrant increased antenatal monitoring or dissuade women from becoming pregnant (Gestational diabetes (GDM)- Preterm birth / premature rupture of membranes-Placenta praevia-Hypertensive disorders and pre-eclampsia-Stillbirth-Caesarean section-Obstetric hemorrhages (placental abruption, ante- and post-partum bleeding) and small for gestational age, admission to NICU, neonatal death) (*low level of evidence, strong recommendation*).[10, 119]

Justification

While several studies have reported a higher morbidity in 2nd/3rd trimester of pregnancy and delivery to be associated with endometriosis, these findings are based on low/moderate quality studies. The discrepancies between the meta-analyses, which are largely based on similar studies but use different inclusion criteria and divergent sub-analysis, limits the implications for clinical practice. Although clinicians should be aware of these potential risks, these findings do currently not warrant increased antenatal monitoring in individuals with endometriosis, as studies on appropriate interventions for risk reduction are lacking.

4. Endometriosis recurrence

4.1 Prevention of endometriosis recurrence:

4.1.1 When surgery is indicated in women with an endometrioma, clinicians should perform ovarian cystectomy, instead of drainage and electrocoagulation, for the secondary prevention of endometriosis-associated dysmenorrhea, dyspareunia, and non-

menstrual pelvic pain. However, the risk of reduced ovarian reserve should be taken into account *(low level of evidence, strong recommendation).*[10, 57, 120, 121]

4.1.2 Clinicians should consider prescribing the postoperative use of a levonorgestrel-releasing intrauterine system (52 mg LNG-IUS) or a combined hormonal contraceptive for at least 18–24 months for the secondary prevention of endometriosis-associated dysmenorrhea (*low level of evidence, strong recommendation*).[10, 120, 122-125]

4.1.3 After surgical management of ovarian endometrioma in women not immediately seeking conception, clinicians are recommended to offer long-term hormone treatment (e.g. combined hormonal contraceptives) for the secondary prevention of endometrioma and endometriosis-associated related symptom recurrence *(very low level of evidence, strong recommendation*).[10, 126, 127]

4.1.4 For the prevention of recurrence of deep endometriosis and associated symptoms, long-term administration of postoperative hormone treatment can be considered *(very low level of evidence, conditional recommendation).*[10, 128, 129]

4.1.5 Long-term administration of progestogen may reduce the recurrence of ovarian endometriotic cysts *(low level of evidence, conditional recommendation)*.[9, 130]

Justification

Cystectomy is probably superior to drainage and coagulation in women with ovarian endometrioma (≥3 cm) with regard to the recurrence of endometriosis-associated pain and the recurrence of endometrioma. A strong recommendation was formulated in favor of cystectomy. Whenever ovarian surgery is performed, the impact on ovarian reserve (i.e., the risk) should be carefully considered against the benefit. Even if efficacy of OCP is documented for dysmenorrhea, it is not confirmed for non-menstrual pelvic pain or dyspareunia. Still, if they do not wish to conceive, women can use regular oral contraceptives for prevention of endometriosis recurrence. For LNG-IUS, evidence shows a positive effect on postoperative pain, disease recurrence, and patients' satisfaction after surgery for endometriosis-associated pain.

Still, there is no overwhelming evidence to support particular treatments over others with the aim of secondary prevention of the disease and of symptoms recurrence (in particular dysmenorrhea). Combined oral contraceptives, preferably in a continuous regimen, and progestins can be considered feasible options as first-line treatments. For both OCP and LNG-IUS, strong recommendations in favor of postoperative therapy were formulated. Still, the choice of intervention should be discussed and decided taking into account patient preferences, costs, availability, risks and side effects. When prescribing such treatment, their contraceptive properties should be considered and weighed against the wishes of the women to become pregnant.

4.2 Treatment of endometriosis recurrence:

4.2.1 Any hormone treatment or surgery can be offered to treat recurring pain symptoms in women with endometriosis *(very low level of evidence, conditional recommendation).*[10, 120, 124, 130-133]

Justification

Although reviews and studies show a benefit of postoperative medical therapy for women with endometriosis, data specified per subtype are scarce. For ovarian endometrioma,

a strong recommendation in favor was considered justified, while for deep endometriosis, only a conditional recommendation could be formulated.

5. Adolescent Endometriosis

5.1 Clinical symptoms

5.1.1 In adolescents, clinicians should take a careful history and consider the following symptoms as suggestive of the presence of endometriosis:

- chronic or a-cyclical pelvic pain, particularly combined with nausea, dysmenorrhea, dyschezia, dysuria, dyspareunia
- cyclical pelvic pain *(very low level of evidence, strong recommendation).* [10, 134-137]

Justification

From the collected data, it can be concluded that a more varied pain pattern is seen in adolescents with endometriosis as compared to adults. Careful history taking and consideration of the differences between adult and adolescent presentation of endometriosis is strongly recommended.

5.2 Clinical examination

5.2.1 In case of virgin written informed consent from the patient and her parents before rectal examination *(GPS).* [10, 138]

5.2.2 The recommendations for clinical examination in adults can be applied *(GPS).* [10, 138]

Justification

No evidence was found with regard to clinical examination in adolescents. Whether vaginal examination and/or rectal examination are acceptable in adolescents should be discussed with the adolescent and her caregiver and may be depending on age and cultural background.

5.3 Imaging

5.3.1 In case of virgin written informed consent from the patient and her parents before rectal u/s *(GPS)*.

5.3.2 Pelvic imaging with ultrasonography, regardless of findings on pelvic examination, also should be considered during evaluation for secondary dysmenorrhea *(GPS)*.

5.3.3 Transvaginal ultrasound is recommended to be used in adolescents in whom it is appropriate, as it is effective in diagnosing ovarian endometriosis (*low level of evidence, strong recommendation).* [10, 136, 138]

5.3.4 If a transvaginal scan is not appropriate, MRI, trans abdominal, transperineal, or trans rectal scan may be considered (*low level of evidence, conditional recommendation)*.[10]

Justification

There is no direct evidence for the role of ultrasound in adolescents. In adults, transvaginal ultrasound showed good mean specificity and sensitivity for detection of ovarian cysts with reasonable confidence intervals and heterogeneity (strong recommendation in favor). In young women, especially those with an intact hymen, a careful approach is

recommended, Transvaginal US may still be an option, but patients should be informed on what to expect, and which other options are available to them.

5.4 Laboratory parameters

5.4.1 Serum biomarkers (e.g., CA-125) are not recommended for diagnosing or ruling out endometriosis in adolescents *(moderate level of evidence, strong recommendation).* [10, 139, 140]

Justification

In adults, clinicians are recommended not to use biomarkers in endometrial tissue, blood, menstrual or uterine fluids to diagnose endometriosis. In adolescents, data support the same conclusion for serum biomarkers, and hence assessment of serum biomarkers is not recommended (*strong recommendation*).

5.5 Diagnostic laparoscopy

5.5.1 In adolescents with suspected endometriosis where imaging is negative and medical treatments (with NSAIDs and/or hormonal contraceptives) have not been successful, diagnostic laparoscopy may be considered (*low level of evidence, conditional recommendation)*.[10, 136, 141]

5.5.2 The appearance of endometriosis may be different in an adolescent than in an adult woman. In adolescents, endometriotic lesions are typically clear or red and can be difficult to identify for gynecologists unfamiliar with endometriosis in adolescents *(GPS)*.[10, 142]

5.5.3 If a laparoscopy is performed, clinicians should consider taking biopsies to confirm the diagnosis histologically, although negative histology does not entirely rule out the disease *(low level of evidence, strong recommendation)*.[10, 143]

Justification

Data in adolescents show that nearly two-thirds of adolescents with CPP or dysmenorrhea have laparoscopic evidence of endometriosis. Laparoscopy to confirm a diagnosis of endometriosis can be considered but should be weighed against the risks of surgery and postoperative complications and can be considered if other diagnostic options cannot be used or have failed, or if medical treatments have not been successful (conditional recommendation). Diagnosis can also be confirmed through history and ultrasound, and treatment should not be withheld for adolescents in which laparoscopic diagnosis was not (yet) performed. Clinicians should be aware that all forms of endometriosis have been found in adolescents, although some reports suggests that peritoneal endometriosis in adolescents may have atypical appearance.

Evidence shows that histological confirmation rate of suspected endometriosis at laparoscopy is high (93%). Also, varying patterns of adolescent endometriosis have been observed. Therefore, if diagnostic laparoscopy is performed, clinicians should consider to taking biopsies to histologically confirm the diagnosis (strong recommendation). Diagnostic laparoscopy with histology is expensive, but accessible and feasible. In performing histological assessment, it should be considered, as in adults, that negative histology does not entirely rule out the disease. This is covered in a good practice point.

5.6 Medical treatment

5.6.1 Nonsteroidal anti-inflammatory drugs should be the mainstay of pain relief for adolescents with endometriosis *(GPS).* [10]

5.6.2 In adolescents with severe dysmenorrhea and/or endometriosis-associated pain, Clinicians should prescribe hormonal contraceptives or progestogens (*very low level of evidence, strong recommendation*).[10, 144, 145]

5.6.3 In adolescents with laparoscopically confirmed endometriosis and associated pain in whom hormonal contraceptives or progestogen therapy failed, clinicians may consider prescribing GnRH agonists for up to 1 year, as they are effective and safe when combined with add-back therapy (*very low level of evidence, conditional recommendation)*.[10, 146]

5.6.4 If GnRH agonist treatment is considered, it should be used only after careful consideration and discussion of potential side effects and potential long-term health risks with a practitioner in a secondary or tertiary care setting (*GPS).*[10, 146, 147]

Justification

Studies on the medical treatment of endometriosis-associated pain are mostly performed in adults. In adolescents, we summarized studies evaluating the use of oral contraceptives, progestogens, and GnRH agonists, from which it can be concluded, also considering indirect data from adults, that these treatments are effective and safe. Considering the possible side effects with regards to BMD and other long term health risks, the GDG recommends prescribing oral contraceptives or progestogens as first line (strong recommendation), and GnRH agonist as second line treatment (conditional recommendation). Although there are no studies evaluating NSAIDs in adolescents with endometriosis-associated pain, data from adults and clinical expertise support a good practice point to consider recommending NSAIDs as an additional treatment option.

5.7 Combined medical and surgical treatment

5.7.1 In adolescents with endometriosis, clinicians should consider postoperative hormone therapy, as this may suppress recurrence of symptoms (*very low level of evidence, strong recommendation*).[10, 148, 149]

Justification

The recommendation to consider postoperative hormone therapy is based on two retrospective studies showing benefit in adolescents on recurrence and disease progression (Doyle*, et al.*, 2009, Seo*, et al.*, 2017). The combination of surgical and medical treatment is expensive, but it is highly accepted by patients and doctors, and in line with management in adults. A strong recommendation in favor of postoperative hormone therapy was formulated.

6. Endometriosis and menopause

6.1 Treatment of endometriosis in postmenopausal women

6.1.1 Clinicians may consider surgical treatment for postmenopausal women presenting with signs of endometriosis and/or pain to enable histological confirmation of the diagnosis of endometriosis (*very low level of evidence, conditional recommendation).*[10, 150-152]

6.1.2 Clinicians should acknowledge the uncertainty towards the risk of malignancy in postmenopausal women. If a pelvic mass is detected, the work-up and treatment should be performed according to national oncology guidelines (*GPS)*.[10, 153, 154]

6.1.3 For postmenopausal women with endometriosis-associated pain, clinicians may consider aromatase inhibitors as a treatment option especially if surgery is not feasible (*very low level of evidence, conditional recommendation).*[10, 151, 152]

Justification

The available, poor-quality evidence from cohort studies show that surgical treatment can improve pain in postmenopausal women with endometriosis. In postmenopausal women with endometriosis, and specifically endometrioma, there seems to be a significant proportion with concordant malignancy. The GDG suggests (conditional recommendation) to consider laparoscopy to treat pain and enable confirmation of the diagnosis of endometriosis.

There are no data on complications of surgery in postmenopausal women, but surgery for endometriosis is considered a relatively safe procedure (see section II.3.a). The benefits of surgical treatment with regards to pain symptoms and to reduce the risk of future malignancy, seem to outweigh the possible complications of surgery.

Although evidence is limited to case reports in postmenopausal women, the efficacy of AIs can be deduced from studies in premenopausal women. Based on the biological aspects, AIs are probably the most appropriate medical treatment for endometriosis-related pain symptoms in postmenopausal women and could be considered a treatment option, for instance when surgery is not feasible, contra-indicated, or when surgery was insufficient to resolve symptoms (conditional recommendation).

6.2 Menopausal symptoms in women with a history of endometriosis

6.2.1 Clinicians may consider combined menopausal hormone therapy (MHT) for the treatment of postmenopausal symptoms in women (both after natural and surgical menopause) with a history of endometriosis (*low level of evidence, conditional recommendation)*.[10, 155, 156]

6.2.2 Clinicians should avoid prescribing estrogen-only regimens for the treatment of vasomotor symptoms in postmenopausal women with a history of endometriosis, as these regimens may be associated with a higher risk of malignant transformation (*low level of evidence, strong recommendation).*[5, 10]

6.2.3 Clinicians should continue to treat women with a history of endometriosis after surgical menopause with combined estrogen-progestogen at least up to the age of natural menopause *(GPS).*[5, 10, 157]

Justification

Efficacy of MHT for the relief of menopausal symptoms in women with endometriosis has not been studied but can be deduced from studies in the general population concluding that MHT is the effective treatment for relieving vasomotor symptoms and urogenital atrophy, with possible beneficial effects on other menopause-related complaints and quality of life. The impact of MHT on recurrence of endometriosis (2 small RCTs, 4 observational studies and 33 case reports) was recently summarized in a systematic review, showing a possibly increased risk. For malignancy, very few cases have been reported for combined MHT or tibolone. Considering the benefits and risks, combined MHT can be considered for the treatment of

postmenopausal symptoms in women with a history of endometriosis (conditional recommendation).

As the reported cases of malignancy could mainly be linked to unopposed estrogens, the risks for estrogen-only regimens seem to outweigh the benefits, and their use should be avoided (strong recommendation).

6.3 Menopause-related major health concerns in women with endometriosis

6.3.1 Clinicians should be aware that women with endometriosis who have undergone an early bilateral salpingo-oophorectomy as part of their treatment have an increased risk of diminished bone density, dementia, and cardiovascular disease. It is also important to note that women with endometriosis have an increased risk of cardiovascular disease, irrespective of whether they have had an early surgical menopause *(GPS).*

Justification

Clinicians should be aware that women with endometriosis who have undergone an early bilateral salpingo-oophorectomy as part of their treatment have an increased risk of diminished bone density, dementia, and cardiovascular disease. It is also important to note that women with endometriosis have an increased risk of cardiovascular disease, irrespective of whether they have had an early surgical menopause.

7. Extra pelvic endometriosis

7.1 Clinicians should be aware of symptoms of extra-pelvic thoracic endometriosis, such as cyclical shoulder pain, cyclical spontaneous pneumothorax, cyclical cough, or nodules which enlarge during menses. (*GPS).*[158-167]

7.2 For abdominal extrapelvic endometriosis, surgical removal is the preferred treatment, when possible, to relieve symptoms. Hormone treatment may also be an option when surgery is not possible or acceptable (*conditional).*[158-167]

7.3 It is advisable to discuss diagnosis and management of extra-pelvic & thoracic endometriosis in a multidisciplinary team in a center with sufficient expertise (*GPS)*.[158-167]

Justification

There is limited evidence on extrapelvic endometriosis. Cyclic pain is the most common presenting symptom, and the diagnosis is usually made by histological confirmation. Additional imaging and endoscopic investigations specific to the location may also be used. MRI provides better contrast resolution than CT and TAS and is superior to CT for depicting the delineation between muscles and abdominal subcutaneous tissues and infiltration of abdominal wall structures. Diagnosis of thoracic endometriosis syndrome is challenging, as these women's symptoms may not immediately be attributed to endometriosis, MRI technique provides a good diagnostic accuracy. As there were no comparative studies identified that compared different imaging modalities, we are unable to determine which imaging tool is optimal for abdominal or thoracic disease

8. Asymptomatic endometriosis

8.1 Clinicians should inform and counsel women about any incidental finding of endometriosis *(GPS)*.[10]

8.2 Clinicians should not routinely perform surgical excision/ablation for an incidental finding of asymptomatic endometriosis at the time of surgery (*very low level of evidence, strong recommendation*).[10]

8.3 Clinicians should not prescribe medical treatment in women with incidental finding of endometriosis (*very low level of evidence, strong recommendation)* [10]

Justification

Based on the lack of evidence and despite the small risk that asymptomatic minimal disease will become symptomatic or progress, the conclusion from the GDG is that medical or surgical treatment of incidental finding of asymptomatic endometriotic lesions is not routinely recommended (strong recommendation). The GDG recommends that clinicians follow national guidelines for the management of ovarian cysts detected incidentally on ultrasound scan.

It is considered good practice to inform and counsel patients about any incidental finding of endometriosis.

8.4 Routine ultrasound monitoring of asymptomatic endometriosis can be considered (*very low level of evidence, conditional recommendation)*. [168]

Justification

Even in the absence of solid data on the benefit of monitoring of asymptomatic endometriosis, the GDG suggests considering US monitoring as it is cost effective and safe (conditional recommendation). There is no information as to how often and how long the monitoring should continue. Alternatively, women with asymptomatic endometriosis can be advised to seek medical help in case of occurrence of any endometriosis-related symptoms.

9. Primary prevention of endometriosis

9.1 Although there is no direct evidence of benefit in preventing endometriosis in the future, women can be advised of aiming for a healthy lifestyle and diet, with reduced alcohol intake and regular physical activity (*low level of evidence, conditional recommendation*). [10, 169-172]

9.2 The usefulness of hormonal contraceptives for the primary prevention of endometriosis is uncertain (*low level of evidence, conditional recommendation*).[10, 173]

Justification

The evidence on a healthy lifestyle and diet, with reduced alcohol intake and regular physical activity for the prevention of endometriosis is summarized in systematic reviews and meta-analyses of epidemiological/observational studies. The benefits of a healthy lifestyle are well known, regardless of endometriosis. To the best of our knowledge, the proposal of healthy lifestyle/diet could be considered a feasible and acceptable option to improve general health, and it may also be beneficial towards the risk of endometriosis. However, the underlying cause of endometriosis remains unknown, thus, due to a lack of scientific data it remains unclear whether preventative measures exist and, if so, how effective they may be.

The evidence on a reduced risk of endometriosis during oral contraceptive use is controversial, as summarized in systematic reviews and meta-analyses of epidemiological/observational studies. To date, it is not possible to exclude the possibility that the apparent protective effect of oral contraceptive against endometriosis is the result of postponement of surgical evaluation due to temporary suppression of pain symptoms.

Implementation considerations

Several barriers may hinder the effective implementation and scale-up of the recommendations in this guideline. These factors may be related to the behaviors of patients (or families), the behavior of healthcare professionals, the organization of care, health service delivery or financial arrangements.

Obstacles to effective implementation include:

- Patient engagement
- Collaboration; person centered, team-based collaboration between clinician, dietitian, pharmacist and others involved in care delivery
- Behavior changes: information, guidance and support delivered easily and consistently can help assess sustained behavioral changes.

Research needs

- Sufficiently powered, prospective, randomized, and ideally blinded studies to determine whether surgical treatment of superficial peritoneal endometriosis improves short- and long-term outcomes, including pain reduction and quality of life.
- Evaluation of the impact of surgery for ovarian and deep endometriosis on natural pregnancy rates in patients without a clear indication for ART, accounting for age, endometrioma characteristics, previous surgeries, adenomyosis, and other fertility-related factors.
- Investigate how the extent of endometriosis affects ART outcomes, to better identify patients who may benefit from ART.
- RCTs to assess whether surgical removal of endometrioma prior to ART improves reproductive outcomes.
- Prospective, long-term studies to explore the association between endometriosis and cancer, using population-based samples, standardized definitions, and comprehensive data collection, while addressing confounders, mediators, and subtype-specific effects by disease and patient characteristics.

Clinical Quality Indicators for Monitoring

Here we will put 3 - 5 quality standards that can be measured and here is what are quality standards and how to write them:

Measuring and monitoring quality of care is recognized as a tool for improving health services and outcomes by healthcare payers and providers throughout the world.

Measuring clinical quality standards in healthcare facilities assesses many aspects of healthcare provided specifically assessing health outcomes, clinical processes, patient safety, efficient use of health care resources, care coordination, and adherence to clinical guidelines.

We will **concentrate on data that can be obtained from the INPATIENT file** of the patient.

A CQS has two main components:

1- **A quality statement** (**QS**): ***a clear and concise sentence taken from the strong recommendations*** describing ***high-priority areas***.

2- A quality measure (**QM**). a ***quantitative measure*** of care quality or service provision specified in the quality statement, and comprise any of three components***: structure, care process or outcome measure***. Quality measures, for process and outcome are specified in the form of a ***numerator and a denominator*** which define a proportion (numerator/denominator). The numerator is assumed to be a subset of the denominator population. For structures, the quality measure is evidence of what the statement refers to.

➢ **Treatment**	
QS.1	Clinicians should use imaging (US or MRI) in the diagnostic work-up, acknowledging that a negative result does not exclude superficial peritoneal disease.
QM.1	Percentage of women with suspected endometriosis who undergo imaging as part of diagnostic work-up, regardless of prior negative imaging.
QS.2	Offer hormone treatment (CHCs, progestogens, GnRH agonists or antagonists) as an option for reducing endometriosis-associated pain.
QM.2	Percentage of patients with endometriosis-associated pain who are offered hormone therapy.
QS.3	Prescribe combined hormonal add-back therapy with GnRH agonists to prevent bone loss and hypoestrogenic symptoms
QM.3	Percentage of patients receiving GnRH agonists who also receive add-back therapy.
QS.4	Perform cystectomy rather than drainage and coagulation during ovarian endometrioma surgery.
QM.4	Percentage of ovarian endometrioma surgeries in which cystectomy is performed.
QS.5	Do not routinely use extended GnRH agonists before ART, as benefit is uncertain.
QM.5	*Percentage of women undergoing ART who are not given pre-treatment GnRH agonists without clear indication*
QS.6	Avoid routine surgery for ovarian endometrioma before ART due to potential harm.
QM.6	*Percentage of women with endometrioma undergoing ART without unnecessary pre-ART surgery*
QS.7	Do not routinely perform surgery before ART in women with rASRM stage I/II endometriosis.
QM.7	*Percentage of early-stage endometriosis patients who proceed to ART without prior surgery*
QS.7	Do not routinely excise or ablate asymptomatic incidental endometriosis during surgery.
QM.7	*Percentage of incidental asymptomatic cases not undergoing surgical excision*

Updating of the guideline

This guideline will be updated whenever there is new evidence.

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