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Endometriosis

Guideline of European Society of Human Reproduction and Embryology

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ESHRE Endometriosis Guideline Development Group

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Introduction

Clinical need

Endometriosis is a chronic inflammatory disease defined as the presence of endometrium-like tissue outside the uterus (Kennedy, *et al.*, 2005). Establishment and growth of such endometriotic tissue is estrogen-dependent (Kitawaki, *et al.*, 2002), 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 (Eskenazi and Warner, 1997, Meuleman, *et al.*, 2009). 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 (Gemmell, *et al.*, 2017, Zondervan, *et al.*, 2020). 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 (Culley, *et al.*, 2013). The same review also reported an impact of infertility and concerns about possible infertility on the patient and the relationship with their partner (Culley, *et al.*, 2013).

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 (Zondervan, *et al.*, 2018). 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.

Previous versions and significant changes

This document is the second update of the ESHRE Guidelines on Endometriosis (Dunselman, *et al.*, 2014, Kennedy, *et al.*, 2005). Where available, peer-reviewed evidence formed the basis of our recommendations. However, there still remain many unanswered questions for which no, or only poor quality or little data are available. We have highlighted such areas by making research recommendations (*see page 18 and 19*) and good practice points that were developed based on clinical expertise by experts in the field of endometriosis and patient representatives.

Whilst most of the more recent studies confirm previous ESHRE recommendations, there are five topics in which significant changes in clinical practice are to be expected. Additionally, some important gaps in the previous version of the guideline have been added. An overview is presented in Table I.

Table I. Overview of changes to the guideline recommendations as compared to the previous version (Dunselman, et al., 2014).

Chapter	Changes in the current version
Diagnosis of endometriosis	! Laparoscopy is no longer the diagnostic gold standard and it is now only recommended in patients with negative imaging results and/or where empirical treatment was unsuccessful or inappropriate.
Treatment of endometriosis-associated pain	! Studies on GnRH antagonist treatments support their use as an additional (second line) treatment option. ! Recent data indicate that postoperative medical treatment may be beneficial towards pain management and support a recommendation to offer it in women not desiring immediate pregnancy. *Danazol and anti-progestogens, laparoscopic uterosacral nerve ablation (LUNA), presacral neurectomy (PSN) and anti-adhesion agents are no longer included in recommendations, but still covered in the text*
Treatment of endometriosis-associated infertility	! The extended administration of GnRH agonist prior to ART treatment to improve live birth rate in infertile women with endometriosis (ultralong protocol) is no longer recommended due to unclear benefits. ! The Endometriosis Fertility Index (EFI) was added as a step in the treatment as it can support decision-making for the most appropriate option to achieve pregnancy after surgery. NEW Information on pregnancy and fertility preservation was added.
Endometriosis recurrence	*Information is included as a separate chapter to highlight its importance and challenges*
Endometriosis and adolescence	NEW This topic was not included in 2014 and is now extensively covered.
Endometriosis and menopause	NEW More extensive information compared to 2014
Asymptomatic endometriosis	*Update without major changes*
Extrapelvic Endometriosis	*Update without major changes*
Primary prevention of endometriosis	*Update without major changes*
Endometriosis and cancer	NEW More extensive information compared to 2014

Target users of the guideline

The guideline covers the care provided by secondary and tertiary healthcare professionals who have direct contact with, and make decisions concerning, the care of women with endometriosis. Although primary healthcare providers are not the main target users of this guideline, it may be of interest for them too.

This guideline is of relevance to European health care providers and women with endometriosis. To assist patient education and shared decision-making, a patient version of this guideline will be developed.

Guideline scope

This guideline offers best practice advice on the care of women with suspected and confirmed endometriosis. 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.

Information on risk factors for endometriosis and associations with other diseases is provided, with recommendations on prevention and monitoring.

Adenomyosis is defined as the presence of ectopic endometrial tissue (endometrial stroma and glands) within the myometrium (International working group of AAGL ESGE ESHRE and WES*, et al.*, 2021). Adenomyosis is not considered a form or subtype of endometriosis and hence not covered in the current guideline. Specific recommendations for management of adenomyosis will be prepared as a separate guidance.

The members of the guideline development group are listed in Annex 1.

Patient population

The current guideline focusses on women with endometriosis; either diagnosed or strongly suspected.

This guideline, in line with endometriosis research, terminology and discussion is focused on females and menstruation. The guideline group recognises that there are individuals living with endometriosis who are transgender, who do not menstruate, who do not have a uterus or who do not identify with the terms used in the literature. For the purposes of this guideline, we use the term “women with endometriosis”, however, it is not intended to isolate, exclude, or diminish any individual’s experience nor to discriminate against any group.

Terminology and definitions

This guideline uses terms and definitions as recently defined in an International Terminology on Endometriosis, published by an international working group of AAGL, ESGE, ESHRE and WES (International working group of AAGL ESGE ESHRE and WES*, et al.*, 2021) . The terminology includes definitions on endometriosis and its subtypes, disease locations, interventions, and outcome parameters.

Endometriosis is defined as a disease characterised by the presence of endometrium-like epithelium and/or stroma outside the endometrium and myometrium, usually with an associated inflammatory process (International working group of AAGL ESGE ESHRE and WES*, et al.*, 2021).

A list of abbreviations used in this document is included in Annex 2.

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List of all recommendations

Diagnosis of endometriosis		Level of evidence[1]	Chapter I
Signs and symptoms			
1	The GDG recommends that 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.		GPP
	Although currently no evidence exists that a symptom diary/questionnaire/app reduces the time to diagnosis or leads to earlier diagnosis, the GDG considers their potential benefit in complementing the traditional history taking process as it aids in objectifying pain and empowering women to demonstrate their symptoms.		GDG STATEMENT
Clinical examination and diagnostic tests			
2	Clinical examination, including vaginal examination where appropriate, should be considered to identify deep nodules or endometriomas in patients with suspected endometriosis, although the diagnostic accuracy is low.	⊕○○○	Strong recommendation
3	In women with suspected endometriosis, further diagnostic steps, including imaging, should be considered even if the clinical examination is normal.	⊕⊕○○	Strong recommendation
4	Clinicians should not use measurement of biomarkers in endometrial tissue, blood, menstrual or uterine fluids to diagnose endometriosis.	⊕⊕⊕○	Strong recommendation
5	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 recommendation
6	In patients with negative imaging results or where empirical treatment was unsuccessful or inappropriate, the GDG recommends that clinicians consider offering laparoscopy for the diagnosis and treatment of suspected endometriosis.		GPP
7	The GDG recommends that laparoscopic identification of endometriotic lesions is confirmed by histology although negative histology does not entirely rule out the disease.		GPP
	Both diagnostic laparoscopy and imaging combined with empirical treatment (hormonal contraceptives or progestogens) can be considered in women suspected of endometriosis. There is no evidence of superiority of either approach and pros and cons should be discussed with the patient.		GDG STATEMENT
8	Follow-up and psychological support should be considered in women with confirmed endometriosis, particularly deep and ovarian endometriosis, although there is currently no evidence of benefit of regular long-term monitoring for early detection of recurrence, complications, or malignancy.	⊕○○○	Weak recommendation
9	The appropriate frequency and type of follow-up or monitoring is unknown and should be individualised based on previous and current treatments and severity of the disease and symptoms.		GPP

[1] The level of evidence reports on the quality of the supporting evidence for each recommendation. More information is available in Annex 4 (page 166). GPP refers to good practice point and is applied for recommendations based primarily on expert opinion.

	Although no adequate studies exist to support the benefits of early versus late diagnosis, the GDG recommends that in symptomatic women, attempts should be made to relieve symptoms, either by empirical treatment or after a diagnosis of endometriosis.		GDG STATEMENT

Treatment of endometriosis-associated pain

Chapter II

Analgesics

10	Women may be offered NSAIDs or other analgesics (either alone or in combination with other treatments) to reduce endometriosis-associated pain.	⊕○○○	Weak recommendation

Hormone treatments

11	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 recommendation
12	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.		GPP
	Combined hormonal contraceptives		
13	It is recommended to prescribe women a combined hormonal contraceptive (oral, vaginal ring or transdermal) to reduce endometriosis-associated dyspareunia, dysmenorrhea, and non-menstrual pain.	⊕⊕○○	Strong recommendation
14	Women suffering from endometriosis-associated dysmenorrhea can be offered the continuous use of a combined hormonal contraceptive pill.	⊕⊕○○	Weak recommendation
	Progestogens (including progestogen-only contraceptives)		
15	It is recommended to prescribe women progestogens to reduce endometriosis-associated pain.	⊕⊕○○	Strong recommendation
16	The GDG recommends that clinicians take the different side effect profiles of progestogens into account when prescribing them.		GPP
17	It is recommended to prescribe women a levonorgestrel-releasing intrauterine system or an etonogestrel-releasing subdermal implant to reduce endometriosis-associated pain.	⊕⊕⊕○	Strong recommendation
	GnRH agonists		
18	It is recommended to prescribe women GnRH agonists to reduce endometriosis-associated pain, although evidence is limited regarding dosage or duration of treatment.	⊕⊕○○	Strong recommendation
19	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.		GPP
20	Clinicians should consider prescribing combined hormonal add-back therapy alongside GnRH agonist therapy to prevent bone loss and hypoestrogenic symptoms.	⊕⊕⊕○	Strong recommendation
	GnRH antagonists		
21	It can be considered to prescribe women GnRH antagonists to reduce endometriosis-associated pain, although evidence is limited regarding dosage or duration of treatment.	⊕⊕⊕○	Weak recommendation
22	The GDG recommends that GnRH antagonists are prescribed as second line (for example if hormonal contraceptives or progestogens have been ineffective) due to their side-effect profile.		GPP
	Aromatase inhibitors		
23	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 antagonists.	⊕⊕○○	Strong recommendation

Surgical treatment

24	It is recommended to offer surgery as one of the options to reduce endometriosis-associated pain.	⊕⊕◯◯	Strong recommendation
25	When surgery is performed, clinicians may consider excision instead of ablation of endometriosis to reduce endometriosis-associated pain.	⊕⊕◯◯	Weak recommendation
	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. 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 labour.		GDG STATEMENT
26	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.	⊕⊕◯◯	Strong recommendation
27	When performing surgery in women with ovarian endometrioma, clinicians can consider both cystectomy and CO_2 laser vaporisation, as both techniques appear to have similar recurrence rates beyond the first year after surgery. Early post-surgical recurrence rates may be lower after cystectomy.	⊕◯◯◯	Weak recommendation
28	When performing surgery for ovarian endometrioma, specific caution should be used to minimise ovarian damage.	⊕◯◯◯	Strong recommendation
29	Clinicians can consider performing surgical removal of deep endometriosis, as it may reduce endometriosis-associated pain and improves quality of life.	⊕⊕◯◯	Weak recommendation
30	The GDG recommends that women with deep endometriosis are referred to a centre of expertise.		GPP
31	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.		GPP
	Due to the heterogeneity of patient populations, surgical approaches, preferences, and techniques, the GDG decided not to make any conclusions or recommendations on the techniques to be applied for treatment of pain associated with deep endometriosis.		GDG STATEMENT
32	Clinicians can consider hysterectomy (with or without removal of the ovaries) with removal all visible endometriosis lesions, in those women who no longer wish to conceive and failed to respond to more conservative treatments. Women should be informed that hysterectomy will not necessarily cure the symptoms or the disease.	⊕⊕◯◯	Weak recommendation
33	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.		GPP
34	The GDG recommends that when hysterectomy is performed, a total hysterectomy is preferred.		GPP
	There are currently no prognostic markers that can be used to select patients that would benefit from surgery. Such markers would need to be assessed prior to surgery and predict a clinically meaningful improvement of pain symptoms.		GDG STATEMENT

Medical therapies as an adjunct to surgery

35	It is not recommended to prescribe preoperative hormone treatment to improve the immediate outcome of surgery for pain in women with endometriosis.	⊕⊕◯◯	Strong recommendation
36	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.	⊕⊕◯◯	Weak recommendation

Medical versus surgical treatment for endometriosis			
37	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 between hormone treatments and surgical treatments for endometriosis-associated pain.		GPP
Non-medical management strategies			
38	The GDG recommends that clinicians discuss non-medical strategies to address quality of life and psychological well-being in women managing symptoms of endometriosis. However, 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.		GPP

Treatment of endometriosis-associated infertility

Chapter III

39	In infertile women with endometriosis, clinicians should not prescribe ovarian suppression treatment to improve fertility.	⊕⊕◯◯	Strong recommendation
40	Women seeking pregnancy should not be prescribed postoperative hormone suppression with the sole purpose to enhance future pregnancy rates.	⊕⊕◯◯	Strong recommendation
41	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.	⊕⊕◯◯	Weak recommendation
42	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 recommendation
43	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.	⊕⊕◯◯	Weak recommendation
44	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.	⊕◯◯◯	Weak recommendation
45	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.	⊕◯◯◯	Weak recommendation
46	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).		GPP
	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.		GDG STATEMENT
Medically assisted reproduction			
47	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.	⊕◯◯◯	Weak recommendation

48	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.	⊕◯◯◯	Weak recommendation
49	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.	⊕⊕◯◯	Weak recommendation
50	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.	⊕◯◯◯	Weak recommendation
51	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.	⊕⊕⊕◯	Weak recommendation
52	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.		GPP
53	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 recommendation
54	There is insufficient evidence to recommend prolonged administration of the COC/progestogens as a pre-treatment to ART to increase live birth rates.	⊕◯◯◯	Weak recommendation
55	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 recommendation
56	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 recommendation
57	Surgery for endometrioma prior to ART can be considered to improve endometriosis-associated pain or accessibility of follicles.		GPP
58	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 recommendation
Non-medical management strategies for infertility			
	Regarding non-medical strategies on infertility, there is no clear evidence that any non-medical interventions for women with endometriosis will be of benefit to increase the chance of pregnancy. 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.		GDG STATEMENT
Fertility Preservation			
59	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 recommendation
Impact of endometriosis on pregnancy and pregnancy outcome			
60	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 recommendation

61	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 centre with appropriate expertise.	⊕○○○	Strong recommendation
	Complications related directly to pre-existing endometriosis lesions are rare, but probably under-reported. Such complications may be related to their decidualisation, adhesion formation/stretching and endometriosis-related chronic inflammation. Although rare, they may represent life-threatening situations that may require surgical management.		GDG STATEMENT
62	Clinicians should be aware that there may be an increased risk of first trimester miscarriage and ectopic pregnancy in women with endometriosis.	⊕⊕○○	Strong recommendation
63	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 recommendation

Endometriosis recurrence

Chapter IV

Prevention of recurrence of endometriosis

64	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 recommendation
65	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 recommendation
66	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 recommendation
67	For the prevention of recurrence of deep endometriosis and associated symptoms, long-term administration of postoperative hormone treatment can be considered.	⊕○○○	Weak recommendation
68	Clinicians can perform ART in women with deep endometriosis, as it does not seem to increase endometriosis recurrence per se.	⊕⊕⊕○	Weak recommendation

Treatment of recurrent endometriosis

69	Any hormone treatment or surgery can be offered to treat recurring pain symptoms in women with endometriosis	⊕○○○	Weak recommendation

Endometriosis and adolescence

Chapter V

Diagnosis

70	In adolescents, clinicians should take a careful history to identify possible risk factors for endometriosis, such as a positive family history, obstructive genital malformations, early menarche, or short menstrual cycle.	⊕○○○	Strong recommendation
71	Clinicians may consider endometriosis in young women presenting with (cyclical) absenteeism from school, or with use of oral contraceptives for treatment of dysmenorrhea.	⊕○○○	Weak recommendation
72	In adolescents, clinicians should take a careful history and consider the following symptoms as suggestive of the presence of endometriosis:	⊕○○○	Strong recommendation

	- chronic or acyclical pelvic pain, particularly combined with nausea, dysmenorrhea, dyschezia, dysuria, dyspareunia - cyclical pelvic pain.		
73	*In the absence of evidence for adolescents specifically, the recommendations for clinical examination in adults can be applied.* The GDG recommends that before performing vaginal examination and/or rectal examination in adolescents, the acceptability should be discussed with the adolescent and her caregiver, taking into consideration the patient's age and cultural background.		GPP
74	Transvaginal ultrasound is recommended to be used in adolescents in whom it is appropriate, as it is effective in diagnosing ovarian endometriosis. If a transvaginal scan is not appropriate, MRI, transabdominal, transperineal, or transrectal scan may be considered.	⊕⊕◯◯	Strong recommendation
75	Serum biomarkers (e.g., CA-125) are not recommended for diagnosing or ruling out endometriosis in adolescents.	⊕⊕⊕◯	Strong recommendation
76	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.	⊕⊕◯◯	Weak recommendation
77	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.	⊕⊕◯◯	Strong recommendation
Treatment			
78	In adolescents with severe dysmenorrhea and/or endometriosis-associated pain, clinicians should prescribe hormonal contraceptives or progestogens (systemically or via LNG-IUS) as first line hormonal hormone therapy because they may be effective and safe. However, it is important to note that some progestogens may decrease bone mineral density.	⊕◯◯◯	Strong recommendation
79	The GDG recommends clinicians consider NSAIDs as treatment for endometriosis-associated pain in adolescents with (suspected) endometriosis, especially if first line hormone treatment is not an option.		GPP
80	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.	⊕⊕◯◯	Weak recommendation
81	The GDG recommends that in young women and adolescents, 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.		GPP
82	In adolescents with endometriosis, clinicians may consider surgical removal of endometriosis lesions to manage endometriosis-related symptoms. However, symptom recurrence rates may be considerable, especially when surgery is not followed by hormone treatment.	⊕◯◯◯	Weak recommendation
83	The GDG recommends that if surgical treatment is indicated in adolescents with endometriosis, it should be performed laparoscopically by an experienced surgeon, and, if possible, complete laparoscopic removal of all present endometriosis should be performed.		GPP
84	In adolescents with endometriosis, clinicians should consider postoperative hormone therapy, as this may suppress recurrence of symptoms.	⊕◯◯◯	Strong recommendation
Fertility preservation			
85	The GDG recommends that adolescents with endometriosis are informed of the potential detrimental effect of ovarian endometriosis and surgery on ovarian reserve and future fertility.		GPP
86	Fertility preservation options exist and the GDG recommends that adolescents are informed about them, although the true benefit, safety, and indications in adolescents with endometriosis remain unknown.		GPP

Endometriosis and menopause			Chapter VI
	Clinicians should be aware that endometriosis, can still be active/symptomatic after menopause.		GDG STATEMENT
Treatment of endometriosis in postmenopausal women			
87	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.	⊕◯◯◯	Weak recommendation
88	The GDG recommends that clinicians 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.		GPP
89	For postmenopausal women with endometriosis-associated pain, clinicians may consider aromatase inhibitors as a treatment option especially if surgery is not feasible.	⊕◯◯◯	Weak recommendation
Menopausal symptoms in women with a history of endometriosis			
90	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.	⊕⊕◯◯	Weak recommendation
91	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 recommendation
92	The GDG recommends that clinicians 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.		GPP
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.		GDG STATEMENT

Extrapelvic Endometriosis			Chapter VII
Diagnosis			
93	Clinicians should be aware of symptoms of extrapelvic endometriosis, such as cyclical shoulder pain, cyclical spontaneous pneumothorax, cyclical cough, or nodules which enlarge during menses.		GPP
94	It is advisable to discuss diagnosis and management of extrapelvic endometriosis in a multidisciplinary team in a centre with sufficient expertise.		GPP
Treatment			
95	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.	⊕◯◯◯	Weak recommendation
96	For thoracic endometriosis, hormone treatment can be offered. If surgery is indicated, it should be performed in a multidisciplinary manner involving a thoracic surgeon and/or other relevant specialists.	⊕◯◯◯	Weak recommendation

Asymptomatic endometriosis

Chapter VIII

Treatment

97	The GDG recommends that clinicians should inform and counsel women about any incidental finding of endometriosis.		GPP
98	Clinicians should not routinely perform surgical excision/ablation for an incidental finding of asymptomatic endometriosis at the time of surgery.	⊕○○○	Strong recommendation
99	Clinicians should not prescribe medical treatment in women with incidental finding of endometriosis.	⊕○○○	Strong recommendation

Monitoring

100	Routine ultrasound monitoring of asymptomatic endometriosis can be considered.	⊕○○○	Weak recommendation

Primary prevention of endometriosis

Chapter IX

101	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.	⊕⊕○○	Weak recommendation
102	The usefulness of hormonal contraceptives for the primary prevention of endometriosis is uncertain.	⊕⊕○○	Weak recommendation
103	Genetic testing in women with suspected or confirmed endometriosis should only be performed within a research setting.		RESEARCH-ONLY

Endometriosis and cancer

Chapter X

104	Clinicians should inform women with endometriosis requesting information on their risk of developing cancer that endometriosis is not associated with a significantly higher risk of cancer overall., Although endometriosis is associated with a higher risk of ovarian, breast, and thyroid cancers in particular, the increase in absolute risk compared with women in the general population is low.	⊕⊕○○	Strong recommendation
105	The GDG recommends that clinicians reassure women with endometriosis with regards to their cancer risk and address their concern to reduce their risk by recommending general cancer prevention measures (avoiding smoking, maintaining a healthy weight, exercising regularly, having a balanced diet with high intakes of fruits and vegetables and low intakes of alcohol, and using sun protection).		GPP
	Based on the limited literature and controversial findings, there is little evidence that somatic mutations in patients with deep endometriosis may be predictive of development and/or progression of ovarian cancer.		GDG statement
106	Clinicians should reassure women with endometriosis about the risk of malignancy associated with the use of hormonal contraceptives.	⊕○○○	Strong recommendation
107	In women with endometriosis, clinicians should not systematically perform cancer screening beyond the existing population-based cancer screening guidelines.	⊕⊕○○	Strong recommendation
108	Clinicians can consider cancer screening according to local guidelines in individual patients that have additional risk factors, e.g., strong family history, specific germline mutations.		GPP
109	Clinicians should be aware that there is epidemiological data, mostly on ovarian endometriosis, showing that complete excision of visible endometriosis may reduce the risk of ovarian cancer. The potential benefits should be weighed against the risks of surgery (morbidity, pain, and ovarian reserve).	⊕⊕○○	Strong recommendation

List of research recommendations

Diagnosis of endometriosis

R1 Randomised research studies are recommended to verify whether symptom diaries or questionnaires lead to improved or earlier diagnosis of endometriosis.

R2 The GDG recommends large, multi-centre prospective studies with independent validation sample sets to investigate the potential benefit of biomarkers in the detection and prognosis of endometriosis.

R3 The GDG recommends research into the development of comprehensive and inclusive consensus criteria for the diagnosis of endometriosis, as an alternative or adjunct to diagnosis via laparoscopy/histology.

R4 The GDG recommends large longitudinal intervention studies to investigate the potential benefits and best long-term management approaches for women with endometriosis.

R5 The GDG recommends large longitudinal studies to investigate the effect of early diagnosis on the quality of life of women with endometriosis.

Treatment of endometriosis-associated pain

R6 Research should investigate the effect of surgery on pain and quality of life (QoL) parameters in different subtypes, preferably via longitudinal population studies.

R7 The GDG recommends sufficiently powered prospective, randomised and ideally blinded studies to unequivocally determine whether surgical treatment of superficial peritoneal endometriosis improves short and long-term clinical outcomes, such as a reduction in pain symptoms and improvement in quality of life.

R8 The GDG recommends that nerve-sparing laparoscopy should be performed in centres of expertise and that data are collected in a standardised fashion to assess its potential benefits and risks.

R9 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.

R10 The GDG recommends sufficiently powered randomised clinical trials in different countries and cultural backgrounds to directly compare the risks, costs, and clinical outcomes of laparoscopy and empirical treatment.

R11 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.

Treatment of endometriosis-associated infertility and Medically assisted reproduction

R12 In patients without a clear indication for ART, the value of surgery for ovarian and deep endometriosis and its effect on natural pregnancy rates should be evaluated. Such studies should consider patient age, endometrioma bilaterality and size, previous surgeries, adenomyosis and other factors affecting fertility.

R13 It is suggested that the EFI is used for better patient phenotyping in studies on surgical treatment and/or the place of MAR in endometriosis-related infertility. The role of the EFI as a pre-surgical triage tool should be validated.

R14 Studies should clarify whether IUI with or without ovarian stimulation is a relevant option for women with (different subtypes of) endometriosis. In addition, the value of EFI to predict the relevance of IUI could be further investigated.

R15 Studies evaluating IUI and ART should report clinically relevant outcomes (live birth rates and cumulative data), and ideally perform subgroup analysis by stage of endometriosis and type of disease.

R16 Further studies of both medical and surgical treatments for endometriosis-associated infertility are required to clarify the relative effectiveness of treatments, in particular trials comparing ART and IUI to other treatments.

R17 The impact of the extent of disease on the outcome of ART should be further studied, as it could provide data for selection of patients that could benefit from ART.

R18 RCTs are required to answer the question whether surgery for endometrioma prior to ART improves reproductive outcomes.

R19 Adequately designed trials are needed to define the magnitude of the benefit of non-medical interventions (nutrition, Chinese medicine, electrotherapy, acupuncture, physiotherapy, exercise, and psychological interventions) in endometriosis-associated infertility. Further research into non-medical interventions for women with endometriosis that employ evidence-based protocols with high intervention integrity is recommended.

Impact of endometriosis on pregnancy and pregnancy outcome

R20 Studies should focus on identification of women with endometriosis who have higher chances of becoming infertile in the future due to endometriosis or endometriosis surgery (and/or who will need ART anyway). These women may have a true benefit from fertility preservation and this evidence would support a future recommendation supporting fertility preservation in selected women with endometriosis.

R21 Observational studies should be conducted to assess natural evolution of pre-existing endometrioma or other endometriosis lesions during pregnancy.

R22 There is a need for prospective, well-designed studies to assess the impact of surgery on subsequent pregnancy evolution, disease phenotype and presence of adenomyosis on the rare complications observed during pregnancy in women with endometriosis.

R23 Larger studies on the evolution of early pregnancy in women with endometriosis versus controls are necessary, particularly with more precise phenotyping including adenomyosis, the role of surgery prior to conception and the mode of conception.

R24 Prospective observational studies are needed in pregnant women with endometriosis versus controls to better define obstetric risks for women with endometriosis and the potential usefulness of interventions to prevent them.

Endometriosis and menopause

R25 More evidence is needed on the efficacy and safety (bone health) of aromatase inhibitors or other medical treatments in postmenopausal women with endometriosis-related pain symptoms.

Extrapelvic Endometriosis

R26 Prospective studies are needed in the field of extrapelvic endometriosis, especially thoracic endometriosis.

Prevention of endometriosis

R27 Research should further consider the genetic background of endometriosis, which may not be a monogenic disorder, and translate findings into validated tests that can be used in diagnosis and prevention.

Endometriosis and cancer

R28 Future studies should investigate the association between endometriosis and cancer using a prospective design, with a long duration of follow-up to take into account the temporality of the association, a population-based sample with standardised collection of data and recognised criteria for the definition of endometriosis, evaluate potential confounding and mediation, and, also importantly, explore heterogeneity by reporting associations according to a) endometriosis and cancer subtypes, and b) patient characteristics (age, menopausal status, etc). When exploring endometriosis macro-phenotypes, results from both exclusive and non-exclusive subtypes should be reported.

R29 More research needs to be performed on the mutational and epigenetic profile of endometriosis tissue, endometrium from endometriosis patients and normal endometrium from women of different ages and reproductive histories. Among women with endometriosis, exclusive macro-phenotypes of endometriosis should be investigated.

R30 More data are needed on the malignant transformation of endometrioma and endometriosis in general to guide the need for monitoring.

I. Diagnosis of endometriosis

The diagnostic delay of endometriosis is a hallmark of a disease that can have at times crippling effects on individuals suffering from its associated symptoms and impact on their lives. However, the growth rate and potential progression pattern of endometriotic lesions, cysts and nodules remain unclear. This is partially the result of a lack of sufficient understanding of the underlying pathophysiology, non-standardised clinical outcome measures and not-fit-for-purpose staging systems. For example, data from women in the placebo arm of medical trials or from those in the sham operation arm of surgical trials suggest that within six to twelve months endometriosis may progress in about one-third of patients whilst similar fractions are seen in non-progressive or even regressive disease (Evers, 2013). However, these reports have to be addressed carefully as the numbers are small and because they do not take into account the biological activity of individual lesions.

There exists no convincing correlation between the extent of the disease categorised by the most widely used revised American Society for Reproductive Medicine (rASRM) classification and the severity of symptoms. Assuming disease progression in at least some individuals, it is conceivable that early diagnosis of endometriosis may also be associated with less extensive disease spread and thus possibly better clinical outcomes, for example reduced anatomical distortion of pelvic and reproductive structures, thus less requirement for MAR, fewer pain episodes etc.

Multiple studies have demonstrated a significant time period between the onset of first symptoms and a reliable diagnosis (Ghai*, et al.*, 2020, Hudelist*, et al.*, 2012, Staal*, et al.*, 2016). These studies rely on data which use mostly surgical confirmation as the gold standard. However, no convincing data exist that take empirical treatment as the potential endpoint into account, i.e., medical treatment for suspected endometriosis. After considering a presumptive diagnosis of endometriosis, the option of further diagnostic confirmation or (empirical) treatment should be discussed. Patient preference is a relevant issue to be considered here. In this respect, diagnosis of certain presentations of endometriosis for example ovarian endometrioma and deep disease by ultrasound or MRI (see below) can be considered without laparoscopy and histological confirmation.

Laparoscopic identification of endometriotic lesions with histological verification has been described as the diagnostic gold standard in the past. (Kennedy*, et al.*, 2005) (Dunselman*, et al.*, 2014). However, advances in the quality and availability of imaging modalities for some forms of endometriosis on the one hand and the operative risk, limited access to highly qualified surgeons and financial implications on the other, call for the urgent need for a refinement of this outdated dogma. Furthermore, development of novel and improvement of existing non-invasive methods to reliably detect or exclude endometriosis is of paramount importance.

Other factors may contribute to the delay including lack of awareness both in the general population but also in the medical community. Despite its high prevalence, the severity of symptoms and its high socioeconomic impact many people have not heard of endometriosis, let alone the association with pain symptoms or infertility. Whilst a few countries have put endometriosis on their national agenda, it is unlikely that public awareness and consequently clinical outcomes will improve unless endometriosis, abnormal menstrual bleeding and pain form a routine part of the school curriculum.

Laparoscopic identification of endometriotic lesions with histological verification has been described as the diagnostic gold standard in the past (Dunselman*, et al.*, 2014, Kennedy*, et al.*, 2005). However, advances in the quality and availability of imaging modalities for at least some forms of endometriosis on the one hand and the operative risk, limited access to highly qualified surgeons and financial implications on the other, calls for the urgent need for a refinement of this dogma. Furthermore,

development of novel and improvement of existing non-invasive methods of reliably detecting or excluding endometriosis is of paramount importance.

I.1. Signs and symptoms

PICO Question: Can clinical symptoms predict the presence of endometriosis?

In a large retrospective analysis of the UK general practice research database concerning the prevalent symptoms within 3 years before the diagnosis of endometriosis (n=5540 each matched (year-of-birth and practice) to four controls), women with subsequent diagnosis of endometriosis had higher proportion of abdominopelvic pain or heavy menstrual bleeding (73 vs. 20%) (Ballard*, et al.*, 2008). When compared with controls, women with endometriosis had odds ratios (OR) for the following symptoms: abdominopelvic pain 5.2 (4.7 to 5.7), dysmenorrhea 8.1 (7.2 to 9.3), heavy menstrual bleeding 4.0 (95%CI 3.5 to 4.5), infertility 8.2 (95%CI 6.9 to 9.9), dyspareunia/postcoital bleeding 6.8 (95%CI 5.7 to 8.2), urinary tract symptoms 1.2 (1.0 to 1.3). In addition, history of being diagnosed with an ovarian cyst 7.3 (95%CI 5.7 to 9.4), with irritable bowel syndrome 1.6 (95%CI 1.3 to 1.8), with pelvic inflammatory disease 3.0 (95%CI 2.5 to 3.6) or with fibrocystic breast disease 1.4 (95%CI 1.2 to 1.7) were risk factors for subsequent diagnosis of endometriosis. Increasing the number of symptoms increased the chance of having endometriosis. Furthermore, women with eventual diagnosis endometriosis had consulted the doctor more frequently and were twice as likely to have had time off from work. Finally, the more symptoms were present, the higher the odds of being diagnosed with endometriosis were (1 symptom: OR 5.0; 95%CI 4.4 to 5.7; 7 symptoms: OR 84.7; 95%CI 58.8 to 121.8) (Ballard*, et al.*, 2008).

A large prospective multi-centre, observational, two-phase study in 13 countries was conducted to generate and validate symptom-based models with the aim to predict endometriosis among symptomatic premenopausal women prior to undergoing their first laparoscopy for pain or fertility investigation (Nnoaham*, et al.*, 2012). The study included clinical symptoms, medical history and preoperative ultrasound findings and was divided into a first phase focussing on model development followed by a second, validation phase. For any (rASRM) stage endometriosis the predictive power of any model without ultrasound was poor (Area under the curve [AUC] 68.3) but could be improved by adding the ultrasound parameter (AUC 80.0). For stage III/IV endometriosis the AUC was reasonable (84.9, with a sensitivity of 82.3% and specificity of 75.8% at optimal cut-off at 0.24) when ultrasound was included (without ultrasound: 83.3, 70.9% and 84.7%, respectively). Whilst these results are not unexpected for stage III/IV endometriosis where ultrasound scan has a high sensitivity and specificity particularly for ovarian endometrioma, the results for endometriosis overall are disappointing (with and without ultrasound scan).

In another prospective study, women undergoing laparoscopy for various gynaecological indications were asked about signs and symptoms including dysmenorrhea, dyspareunia, non-cyclical pelvic pain, and infertility. However, none of these symptoms were predictive of endometriosis (Eskenazi*, et al.*, 2001).

Forman *et al*. found in a prospective study in women undergoing laparoscopy for subfertility that only severe dysmenorrhea was predictive of endometriosis (RR 1.7) supporting other studies that increased severity of dysmenorrhea may indicate the presence of endometriosis (Eskenazi*, et al.*, 2001, Forman*, et al.*, 1993, Hsu*, et al.*, 2010).

Recommendation (1)

The GDG recommends that 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.	GPP

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.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question I.1)

PICO QUESTION: DOES THE USE OF SYMPTOM DIARIES OR QUESTIONNAIRES COMPARED TO TRADITIONAL HISTORY TAKING LEAD TO IMPROVED OR EARLIER DIAGNOSIS OF ENDOMETRIOSIS?

Pain is a cardinal symptom for many individuals suffering from endometriosis. Pain perception can vary individually in intensity, location, time of occurrence and duration. In addition, pain quality and associated sympathetic and parasympathetic reactions may differ at times. Getting a doctor's appointment can often take many weeks or even months after the onset of the pain symptoms. As such, some patients present with summaries of their symptomatic experiences to their appointment in the form of a diary or by answering a questionnaire.

Pain symptoms in endometriosis patients are rather unspecific and their severity does generally not correlate well with the extent of disease according to the widely used rASRM classification system (Vercellini*, et al.*, 2007). This may be a reflection of the limitation of this and other available staging systems which are primarily designed to describe disease extent and location for surgical purposes and do not take biological aspects such a disease activity into account (Johnson*, et al.*, 2017). Other staging systems await large scale validation (Haas*, et al.*, 2013).

There exists an unmet clinical need for a reproducible and easy-to-use objective patient-reported outcome (PRO) tool of endometriosis-associated symptoms primarily for therapeutic studies (Gater*, et al.*, 2020, Jones*, et al.*, 2006). Similarly, such measures may prove helpful in advancing diagnostic accuracy of existing methods and avoid inter- and intra-rater variability (Deal*, et al.*, 2010, van Nooten*, et al.*, 2018, Wyrwich*, et al.*, 2018). Whilst there are different PRO tools available, to date no study has assessed whether their use or the use of symptom diaries compared to traditional history taking techniques has shortened or improved the diagnosis of endometriosis neither for screening nor for triaging of symptomatic patients (Surrey*, et al.*, 2017). However, it is likely that objective assessment tools will facilitate large scale studies into this.

Conclusion

Although currently no evidence exists that a symptom diary/questionnaire/app reduces the time to diagnosis or leads to earlier diagnosis, the GDG considers their potential benefit in complementing the traditional history taking process as it aids in objectifying pain and empowering women to demonstrate their symptoms.

Research recommendation (R1)

Randomised research studies are recommended to verify whether symptom diaries or questionnaires lead to improved or earlier diagnosis of endometriosis.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question I.2)

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I.2. Diagnostic work-up

I.2.a Clinical examination

PICO QUESTION: DOES CLINICAL EXAMINATION OF SYMPTOMATIC WOMEN RELIABLY PREDICT THE PRESENCE OF ENDOMETRIOSIS?

Endometriosis is predominantly an intra-abdominal disease (for extrapelvic endometriosis, see Chapter VII). Clinical examination in women suspected with abdominal endometriosis includes physical examination of the pelvis but also the inspection and palpation of the abdomen with the aim to facilitate diagnosis and to optimise treatment decisions. Where appropriate, vaginal inspection should include a speculum as well as bimanual and rectovaginal palpation (Bazot*, et al.*, 2009, Chapron*, et al.*, 2002). A prospective study has demonstrated that reliability of the clinical examination in detecting pelvic endometriosis is improved during menstruation (Koninckx*, et al.*, 1996).

For women with peritoneal endometriosis and adhesions one study suggested a similar diagnostic accuracy of bimanual examination and transvaginal ultrasound in women with an immobile uterus and adnexal mass or tenderness (Nezhat*, et al.*, 1994). Uterine mobility or rather a lack thereof was found as a predictive marker in another retrospective study of almost 800 infertile women with surgically confirmed endometriosis (Khawaja*, et al.*, 2009). In another retrospective study of 284 women with chronic pelvic pain, anterior vaginal wall tenderness had a sensitivity of 17% in women with endometriosis without interstitial cystitis (Paulson and Paulson, 2011).

In a prospective study involving 129 women with superficial, ovarian, and deep endometriosis, the prevalence and accuracy of diagnosing endometriosis by clinical examination were investigated. The sensitivity/specificity were reported for endometriosis on the ovary 44%/99%, uterosacral ligaments 50%/80%, pouch of Douglas 76%/92%, vagina 73%/98%, rectovaginal space 78%/98%, urinary bladder 25%/100%, and rectosigmoid 39%/97%, respectively.. Values for transvaginal ultrasound (TVUS) were similar for most locations but were superior to vaginal examination in cases of ovarian, uterosacral ligament and rectosigmoid endometriosis (Hudelist*, et al.*, 2011).

For deep endometriosis, vaginal examination can facilitate the detection of infiltration or nodules of the vagina, uterosacral ligaments, or pouch of Douglas, whereas sensitivity was poor for endometriosis of the vagina, uterosacral ligaments, rectovaginal septum, and intestine (50%, 73%, 18% ad 46%, respectively) (Bazot*, et al.*, 2009).

Rectovaginal digital examination may allow the detection of infiltration or mass involving the rectosigmoid colon or adnexal masses (Bazot*, et al.*, 2009, Condous*, et al.*, 2007, Eskenazi*, et al.*, 2001, Koninckx*, et al.*, 1996, Ripps and Martin, 1992).

Recommendations (2-3)

Clinical examination, including vaginal examination where appropriate, should be considered to identify deep nodules or endometriomas in patients with suspected endometriosis, although the diagnostic accuracy is low.	⊕◯◯◯

In women with suspected endometriosis, further diagnostic steps, including imaging, should be considered even if the clinical examination is normal.	⊕⊕◯◯

Justification

Overall, the evidence suggests that clinical examination of symptomatic women does not reliably predict the presence of endometriosis in the abdomen and pelvis.

In the first (strong) recommendation, the GDG weighed the benefits of clinical examination versus the burden for patients. Clinical examination may be useful for a diagnosis of endometriosis and/or other diseases and it may lead to further, more specific diagnostic approaches e.g., using medical technologies (see below). The financial burden of clinical examination is minimal as it can be performed at low costs. In the second (strong) recommendation, further diagnostic steps are recommended. The evidence level for this recommendation is derived from the evidence for diagnostic imaging.

Vaginal and/or rectovaginal examination might be inappropriate in certain situations and in adolescents. Furthermore, it can be very painful in some women. In these women, with high burden/discomfort (adolescents, due to religion, painful examination, sexual abuse in the past, virgo intacta etc.) vaginal examination should ideally be omitted and other medical technologies, as described below, should be used as a first step towards diagnosis. Clinical examination in adolescence is discussed in chapter V.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question I.3)

I.2.b Medical technologies

PICO Question: Are medical technologies reliable in diagnosing endometriosis and establishing the extent of the disease?

The significant delay in diagnosing endometriosis is ubiquitously evident and poses an enormous burden on affected women worldwide. Currently, pelvic/abdominal disease is clinically subdivided into superficial (peritoneal/serosal) lesions, ovarian endometriosis cysts (endometrioma) and deep endometriosis (by arbitrary definition more than 5 mm below the serosal/peritoneal surface) (Cornillie*, et al.*, 1990). However, it is likely that with further insight into the underlying disease processes using new technologies and large-scale studies, in the future more distinct classification systems will emerge with the aim of improving both diagnostic accuracy and therapeutic efficacy.

Medical technologies are successfully used in many conditions to identify or rule out disease. Similarly, such approaches have been studied in endometriosis patients. These include imaging technologies, biomarkers, and surgery alone and in combination. Applying imaging methods and the interpretation of their results can be dependent on a clinician's experience and skill (e. g. ultrasound, surgery) and the availability of the imaging equipment (e. g. MRI). Thus, the transferability of data from published studies performed by experts to the general medical community has to be considered and potentially adapted to the local situation. Similarly, biomarkers require standardised collection and storage protocols for biological samples, accompanying clinical and surgical data needs to be of the highest standard using evidence-based tools (Becker*, et al.*, 2014, Casper, 2014, Fassbender*, et al.*, 2014, Rahmioglu*, et al.*, 2014, Vitonis*, et al.*, 2014) and clinical studies adequate outcome measures (Duffy*, et al.*, 2020).

Over the years, a dogma has emerged that a laparoscopy is the gold standard to diagnose endometriosis. However, although routinely performed in most countries, it remains an invasive procedure with potential morbidity and even mortality (Byrne*, et al.*, 2018a, Chapron*, et al.*, 1998). Thus, a reliable, ideally inexpensive non-invasive approach with high sensitivity and specificity would be the preferable approach. To move away from the reliance of invasive diagnostic means such as

laparoscopy, large scale international, multi-centre studies are urgently needed using novel technological platforms, meticulous standardised phenotyping, sufficient funding and an open mind.

I.2.b.1 Biomarkers

There exists a multitude of published studies which tested potential biological markers for their predictability of the presence or absence of endometriosis, mostly in symptomatic patients. It is highly likely that negative results could not be published suggesting a high rate of publication bias in this field. May *et al*. first systematically summarised the available data on potential blood, urine, and endometrial biomarkers (May*, et al.*, 2010, May*, et al.*, 2011). A recently updated review of available studies using the Cochrane Collaboration tool set confirmed the initial findings that currently there are no reliable biomarkers available for clinical use (Gupta*, et al.*, 2016, Liu*, et al.*, 2015, Nisenblat*, et al.*, 2016a). Unfortunately, all studies included were found to be of poor methodological quality. The group assessed these studies for their value as a replacement or triage test against the existing standard of laparoscopy (Wykes*, et al.*, 2004).

For blood tests, the authors concluded that, although a subset of biomarkers could prove useful in detecting endometriosis or differentiating ovarian endometrioma from other ovarian tumours, there was insufficient evidence to draw meaningful conclusions (Nisenblat*, et al.*, 2016a).

Similarly, studies on urinary markers did not show sufficient quality for recommendation for routine clinical use (Liu*, et al.*, 2015).

The group then looked at available studies on endometrial markers. A meta-analysis of seven studies found, that the histological assessment of the neuronal marker protein gene product 9.5 (PGP 9.5) would potentially meet the criteria for a replacement test for laparoscopy (sensitivity 0.96; 95%CI 0.91 to 1.00; specificity 0.86; 95%CI 0.70 to 1.00)(Gupta*, et al.*, 2016). However, the studies demonstrated considerable heterogeneity. Other neuronal markers including vasoactive intestinal polypeptide (VIP), substance P (SP), neuropeptide Y (NPY), calcitonin gene-related peptide (CGRP), and a combination of PGP 9.5, SP, and VIP were thought to show promise as potential markers, but the evidence was either poor quality or insufficient (Gupta*, et al.*, 2016).

Another systematic review assessed the diagnostic accuracy of CA-125 for endometriosis (Hirsch*, et al.*, 2016). This review included 19 prospective and three retrospective observational studies involving a total of 3626 participants. By including only studies with histologically confirmed endometriosis as the reference standard using a threshold of 30 units/ml, Hirsch *et al*. calculated a pooled specificity of 93% (95%CI 89 to 95%), but only a sensitivity of 52% (95%CI 38 to 66%) for all endometrioses. Previously, Mol *et al.,* by focussing on women undergoing fertility and pelvic pain investigation, found that the performance of serum CA-125 was low to detect any form of endometriosis, but better for stage III/IV endometriosis (Mol*, et al.*, 1998). The latter finding was also confirmed in a systematic review and meta-analysis (Hirsch*, et al.*, 2016). However, Mol *et al*. also included studies with only visual confirmation of endometriosis which may partially explain the lower performance (Fernando*, et al.*, 2013, Kazanegra*, et al.*, 2008).

More recently, miRNAs which are known to regulated genes crucial for processes involved in the pathogenesis of endometriosis have been assessed for their clinical potential as biomarkers. A pilot study was followed by a small validation study assessing the use of a microRNA panel as a non-invasive diagnostic method for detecting endometriosis (Cosar*, et al.*, 2016, Moustafa*, et al.*, 2020). Serum from women undergoing surgery for suspected benign indications was tested for miR-125b-5p, miR-150-5p, miR-342-5p and miR-451a. Using an algorithm for combining the expression values this set of miRNAs could differentiate between 41 women with confirmed endometriosis and 59 controls and confirmed in an independent but previously used data set (n=24 for both groups). Interestingly, neither menstrual

status nor hormonal medication appeared to influence the outcome significantly, although the number of included participants in these subgroup analyses was very small. Overall, confirmation in larger, independent studies is required before routine clinical use can be advised. In another study set using sequencing, model building and then testing of the model identified miRNAs failed the test of validation (Vanhie*, et al.*, 2019).

Recommendation (4)

Clinicians should not use measurement of biomarkers in endometrial tissue, blood, menstrual or uterine fluids to diagnose endometriosis.	⊕⊕⊕○

Justification

Overall, no biological markers currently exist that reliably can rule in and rule out endometriosis.

From the literature, CA-125 can be considered as a screening marker for symptomatic patients, it is also inexpensive and widely available. It may convince primary care physicians that endometriosis is a possible reason for the symptoms prompting further investigation.

However, a negative result does not rule out the disease which bears the risk that patients who have a negative CA-125 are dismissed. Furthermore, it is considered that even a positive test is not clinically relevant, and may cause anxiety in the patient, and possible overtreatment. As such, CA-125 testing is not considered relevant in the diagnosis of endometriosis.

Research recommendation (R2)

The GDG recommends large, multi-centre prospective studies with independent validation sample sets to investigate the potential benefit of biomarkers in the detection and prognosis of endometriosis.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question I.4)

I.2.b.2 Imaging techniques in the diagnosis of endometriosis

Imaging techniques commonly applied in benign gynaecology include (where appropriate) transvaginal ultrasound scan (US) and magnetic resonance imaging (MRI). Whilst most ultrasound scans are part of routine initial investigations in primary care, more advanced ultrasound scan and MRIs are usually only available through secondary and tertiary care routes.

As part of a set of Cochrane reviews on diagnostic tools for endometriosis, existing evidence of various imaging modalities for the non-invasive diagnosis of endometriosis was published in 2016 (Nisenblat*, et al.*, 2016b). The diagnostic accuracy of superficial, ovarian, and deep endometriosis was compared with surgical diagnosis as a reference standard. Altogether, results from 49 studies involving 4807 women were included.

Pelvic (superficial) endometriosis:

For overall pelvic endometriosis, none of the imaging modalities showed superior sensitivity and specificity to laparoscopy (Wykes*, et al.*, 2004). Reported findings were heterogeneous with wide confidence intervals. However, transvaginal ultrasound scan showed good specificity (95%; 95%CI 89 to 100%), but poor sensitivity (65%; 95%CI 27% to 100%). MRI showed both poor specificity and sensitivity (72% and 79%, respectively) as well as strong heterogeneity between studies. Two small studies, included in the review, using 3.0 tesla MRI reported specificity of 100% and sensitivity between 81-95% (Manganaro*, et al.*, 2012, Thomeer*, et al.*, 2014). However, because of the small size of the studies and large confidence intervals interpretation of the data was cautioned. Studies using other imaging techniques such as PET-CT did not meet inclusion criteria (Nisenblat*, et al.*, 2016b).

Ovarian endometriosis (endometrioma):

For ovarian endometriotic cysts, studies assessing transvaginal ultrasound showed good mean specificity and sensitivity with reasonable confidence intervals and heterogeneity (specificity 96%, 95%CI 92 to 99%; sensitivity 93%, 95%CI 87 to 99%) (Nisenblat*, et al.*, 2016b).

For MRI, mean specificity and sensitivity were similar to those from transvaginal ultrasound scan studies (91% and 95%, respectively). One study compared MRI directly with transvaginal and transrectal ultrasound (Bazot*, et al.*, 2009). Whilst transrectal ultrasound scan had a lower specificity and sensitivity (77% and 89%, respectively), results for transvaginal ultrasound (86% and 94%, respectively) and MRI (88% and 92%, respectively) were similarly promising.

Deep endometriosis

Deep endometriosis can involve many areas in the pelvis such as visceral organs (e.g., bowel, bladder), the pelvic wall and its retroperitoneal structures (ureters, nerves, blood vessels etc.). For transvaginal ultrasound (including conventional ultrasound, 3-D ultrasound and sonovaginography) overall specificity and sensitivity estimates have been reported as 94% and 79%, respectively, whereas sensitivity may be slightly improved with 3-D ultrasound (87%) (Guerriero*, et al.*, 2014). However, no data were available on the minimum size of the lesions detectable. Furthermore, even in experienced hands both sensitivity and specificity can vary depending on the location of the disease in the pelvis with the poorest accuracy probably for deep endometriosis involving either uterosacral ligaments or the vagina (Bazot*, et al.*, 2009).

Studies assessing the role of MRI in diagnosing deep endometriosis of the pelvis reported an overall mean specificity of 77% (95%CI 44 to 100%) and a mean sensitivity of 94% (95%CI 90 to 97%) (Nisenblat*, et al.*, 2016b).

Deep endometriosis; Rectosigmoid

For endometriosis of the rectosigmoid a more recent systematic review of eight studies comparing MRI and transvaginal US reported a pooled specificity and sensitivity for MRI of 96% (95%CI 94 to 97%) and 90% (95%CI 87 to 92%), respectively, and for transvaginal ultrasound 96% specificity (95%CI 94 to 97%) and 90% sensitivity (95%CI 87 to 92%). There was no significant difference between both methods (Moura*, et al.*, 2019).

Overall, these data suggest that transvaginal ultrasound and MRI have a similar or slightly better specificity and sensitivity than surgery for ovarian and deep endometriosis. When it comes to superficial disease, these or any other imaging modalities do not seem to have a superior diagnostic value compared to laparoscopic surgery (Wykes*, et al.*, 2004). However, one has to take a few points into account when addressing the question of whether imaging should replace surgery as the gold standard for endometriosis. Firstly, the results from the systematic review by Wykes *et al.,* which is often used as the standard, are based on four studies including 413 patients. Secondly, in the published studies, imaging was performed by experts in the field and therefore the results have to be interpreted with caution when they are translated into real world scenarios, even if this applies to both approaches (US and MRI). Thirdly, the methodological quality of some of the data were generally deemed as low and only few studies could be included in the systematic reviews. Fourthly, one has to take into account the pros and cons of an invasive procedure such as a laparoscopy (e.g., the associated morbidity and mortality) versus the possibility of treatment and empowerment of women who have been suffering from often debilitating symptoms to objectify and demonstrate the disease. Costs, availability of equipment and expertise for both imaging and surgery need to be included into the decision-making process.

Recommendations (5-7)

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.	⊕⊕◯◯
In patients with negative imaging results or where empirical treatment was unsuccessful or inappropriate, the GDG recommends that clinicians consider offering laparoscopy for the diagnosis and treatment of suspected endometriosis.	GPP
The GDG recommends that laparoscopic identification of endometriotic lesions is confirmed by histology although negative histology does not entirely rule out the disease.	GPP

Justification

Taking the factors discussed by Wykes *et al.* and 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. The GDG formulated a strong recommendation for using imaging in the diagnostic work-up with a sidenote on false-negative results. Two further good practice points were formulated to support clinical practice.

Research recommendation (R3)

The GDG recommends research into the development of comprehensive and inclusive consensus criteria for the diagnosis of endometriosis, as an alternative or adjunct to diagnosis via laparoscopy/histology.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question I.4)

I.2.c Diagnostic laparoscopy or empirical treatment

PICO Question: Does diagnostic laparoscopy compared to empirical medical treatment result in better symptom management in women suspected of endometriosis?

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 (Zondervan*, et al.*, 2020).

There exists the widespread concept that laparoscopy is the accepted standard to diagnose abdominal endometriosis which was formulated in the first edition of this guideline (Kennedy*, et al.*, 2005). 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 (Bafort*, et al.*, 2020, Byrne*, et al.*, 2018b, Chapron*, et al.*, 1998).

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 (Kuznetsov*, et al.*, 2017). 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.

Conclusion

Both diagnostic laparoscopy and imaging combined with empirical treatment (hormonal contraceptives or progestogens) can be considered in women suspected of endometriosis. There is no evidence of superiority of either approach and pros and cons should be discussed with the patient.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question I.5).

I.3. Long term monitoring

PICO QUESTION: IS LONG TERM MONITORING OF WOMEN WITH ENDOMETRIOSIS BENEFICIAL IN PREVENTING ADVERSE OUTCOMES (RECURRENCE, COMPLICATIONS, MALIGNANCY) ?

In order to answer the question whether long term monitoring of women with endometriosis is beneficial, one needs to understand the natural course of the disease. Endometriosis is generally considered to have a chronic course. However, there exist only few reports on disease progression. Women included in clinical trials for medical or surgical treatment who were randomised to the placebo/sham operation arm of the studies had progression (higher rASRM score) in approximately 29% of cases at second look laparoscopy after 3-6 months (Evers, 2013). No change or a lower rASRM score were reported in 29% and 42%, respectively.

Irrespective of treatment approach, data suggest a recurrence rate of 20-50% within five years (Guo, 2009). However, data on whether these numbers constitute recurrence of symptoms and/or disease remains unclear.

Whilst an ovarian endometrioma can be monitored fairly easily by ultrasound, superficial peritoneal disease is usually not detectable without surgery. In addition, as neither the occurrence, magnitude nor the speed of any change in disease extent is clear and the correlation between disease stage and symptom severity is poor, the question arises whether monitoring of endometriosis is feasible and of any benefit. Early detection could lead to early and potentially less complex treatment and potentially a reduced risk of the development of chronic pain. On the other hand, it could lead to unnecessary additional invasive procedures and treatment side effects.

In a small study evaluating the potential use of serial CA-125 serum concentrations to monitor endometriosis, a subgroup of women had a second look laparoscopy. In 24/26 of these women changes in CA-125 correlated with surgical findings (Pittaway, 1990). Matalliotakis *et al*. monitored CA-125 in women with endometriosis who were treated with Danazol and found a significant reduction of serum levels after 3 months of treatment. However, no confirmation/change of disease status was reported (Matalliotakis*, et al.*, 1994).

Another group used serum CA-125 levels as a surrogate marker for disease progression (Chen*, et al.*, 1998). Involving 75 women with 'advanced' endometriosis who were treated with surgery and postoperative danazol, the authors concluded that CA-125 was not a reliable marker to monitor therapy. However, in a small subset of patients who underwent second look laparoscopy after one year, CA-125 levels were higher in women with recurrence (n=15) than in those without recurrent endometriosis (n=9).

Endometriosis can have a different effect on each individual. Therefore, monitoring should not be purely focussed on imaging and blood tests. Physical examination and assessment of the mental impact should be considered.

Recommendations (8-9)

Follow-up and psychological support should be considered in women with confirmed endometriosis, particularly deep and ovarian endometriosis, although there is currently no evidence of benefit of regular long-term monitoring for early detection of recurrence, complications, or malignancy.	⊕◯◯◯

The appropriate frequency and type of follow-up or monitoring is unknown and should be individualised based on previous and current treatments and severity of the disease and symptoms.	GPP

Justification

There currently exist no studies of sufficient quality or size to address the question of whether patients with endometriosis should be monitored long term.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question I.6)

Research recommendation (R4)

The GDG recommends large longitudinal intervention studies to investigate the potential benefits and best long-term management approaches for women with endometriosis.

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I.4. Impact of the time of diagnosis on quality of life

NARRATIVE QUESTION: DOES EARLY DIAGNOSIS OF ENDOMETRIOSIS VERSUS LATE DIAGNOSIS LEAD TO BETTER QUALITY OF LIFE?

In many cases, endometriosis can have a detrimental effect on the lives of affected women, their partners, and families (Culley*, et al.*, 2013b). The negative impact of endometriosis-associated symptoms is complex and multidimensional which should be assessed using validated tools (Jones*, et al.*, 2004, Jones*, et al.*, 2001). A retrospective 15-year follow-up study demonstrated that half of women with surgically confirmed endometriosis reported a negative impact on different aspects of their life (education, work ability, relationship, and social life) (Ballard*, et al.*, 2006). It is conceivable that an early diagnosis, ideally followed by early, adequate treatment will reduce pain, reduce the risk of infertility, and deliver patients an explanation for their symptoms. To date, no adequate studies so far exist assessing whether an early versus late diagnosis leads to change in quality of life. However, women may experience benefits from the diagnosis (and adequate treatment) of endometriosis. Qualitative studies have demonstrated that diagnosis of the disease can result in feelings of relief, legitimation, liberation and empowerment as it can enable women and their partners to better understand the reason for their symptoms, to accept the situation and to be able to make sense of their circumstances. Furthermore, reliably identifying endometriosis may have other, far-reaching consequences including enhanced access to support services and awareness in the workplace which may lead to positive adjustments improving not only the lives of affected women but also of employers by managing expectations and goals (Culley*, et al.*, 2013a, Culley*, et al.*, 2013b).

Conclusion

Although no adequate studies exist to support the benefits of early versus late diagnosis, the GDG recommends that in symptomatic women, attempts should be made to relieve symptoms, either by empirical treatment or after a diagnosis of endometriosis.

Research recommendation (R5)

The GDG recommends large longitudinal studies to investigate the effect of early diagnosis on the quality of life of women with endometriosis.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question I.7)

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II. Treatment of endometriosis-associated pain

Women with endometriosis are confronted with one or both of two major problems: endometriosis-associated pain and infertility. This section focuses on pain treatment; chapter III addresses treatment of women suffering mainly from infertility.

Endometriosis-associated pain includes dysmenorrhea, dyspareunia, dysuria, dyschezia, and non-menstrual pelvic pain (see section I.1). Signs and symptoms), but the literature searches were not restricted to these terms. In the searches, quality of life was included, although this was found as an outcome in only a limited number of studies.

This chapter on the treatment of endometriosis-associated pain is subdivided into sections on empirical treatment, medical treatment, surgical treatment, pre- or postoperative medical treatment (including secondary prevention after surgery) and non-medical management strategies. It has to be noted that endometriosis is a chronic and incurable disease in a significant number of women. The treatments described in this section can offer (partial, often only temporary) relief of pain symptoms, but symptoms often recur after discontinuation of therapy.

II.1. Analgesics

PICO Question: Are analgesics effective for symptomatic relief of painful symptoms associated with endometriosis ?

Most women with suspected or known endometriosis who would like pharmacological analgesia will buy over-the-counter medications or be prescribed simple analgesics, such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs). However, the available evidence to support their use is of very low quality and based on one study (Brown*, et al.*, 2017, Kauppila and Ronnberg, 1985). There is also some limited evidence that NSAIDs might inhibit ovulation if taken continuously during the cycle (making conception less likely) (Norman, 2001).

Neuromodulators (e.g., anti-depressants, selective serotonin uptake inhibitors or anticonvulsants) are used mainly by pain medicine specialists and primary care physicians in the management of chronic or persistent pain. Neuromodulators differ from conventional analgesics, such as NSAIDs, in that they primarily affect the central nervous system's modulation of pain rather than peripheral meditators of inflammation. Tricyclic antidepressants (e.g., amitriptyline, nortriptyline), selective serotonin uptake inhibitors (e.g., duloxetine) and anticonvulsants (e.g., gabapentin and pregabalin) have all shown promise in the treatment of endometriosis-associated pain. However, in randomised clinical trials for the management of chronic pelvic pain, they have not been proven to be clearly superior to placebo and are sometimes associated with severe, dose-limiting side effects (Horne*, et al.*, 2020).

Recommendation (10)

Women may be offered NSAIDs or other analgesics (either alone or in combination with other treatments) to reduce endometriosis-associated pain.	⊕◯◯◯

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 sensitisation). 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 (weak recommendation).

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question II.1).

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II.2. Hormone treatments

PICO QUESTION: ARE HORMONE THERAPIES EFFECTIVE FOR PAINFUL SYMPTOMS ASSOCIATED WITH ENDOMETRIOSIS?

Hormone therapy is based on the evidence that endometriosis is a 'steroid dependent' condition. Treatments are often started when endometriosis is suspected in young women prior to surgical confirmation of lesions and are also offered after surgery when symptoms persist after surgical intervention e.g., for persistent or recurrent disease. The most commonly prescribed treatments for endometriosis include drugs that modify the hormonal environment either by suppressing ovarian activity or acting directly on steroid receptors and enzymes found in the lesions. These include progestogens, anti-progestogens, combined oral contraceptives, gonadotrophin releasing hormone (GnRH) agonists, GnRH antagonists, the levonorgestrel intrauterine system (LNG-IUS), danazol and aromatase inhibitors (e.g., letrozole).

All of the above hormone treatments lead to a clinically significant reduction in pain when compared to placebo (when visual analogue scales for dysmenorrhea and non-menstrual pelvic pain are used) (National Institute for Health and Care Excellence, 2017). In clinical trials, the magnitude of this treatment effect has been shown to be similar for all treatments, (suggesting that there is little difference between them in their capacity to reduce pain) and none of the hormone treatments free of side effects. In clinical practice, the efficacy and side-effect profiles of these therapies are highly individual, and unfortunately finding a good therapy is often 'trial and error'.. In addition, the contraceptive properties of the hormones may be unwanted if fertility is an issue, or may be welcome, if the woman does not wish to become pregnant.

Recommendations (11-12)

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.	⊕⊕⊕○

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.	GPP

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 (strong recommendation). 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.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question II.2).

II.2.a. Combined hormonal contraceptives.

II.2.a.1 Efficacy (dyspareunia, dysmenorrhea, and non-menstrual pain)

The data on the efficacy of the combined oral contraceptive pill (OCP) on endometriosis-related pain have recently been summarised in three systematic reviews.

The review of Grandi *et al*, summarizing data on several OCPs but also other agents such as progestin only contraceptives, concluded that OCPs result in a statistically significant reduction in endometriosis-related pain, resulting in improvement in quality of life (QoL) (Grandi*, et al.*, 2019).

The review of Jensen *et al.* included RCTs and other studies and concluded that OCP treatment results in clinically important and statistically significant reductions in endometriosis-related pain. They reported clinically significant reductions in dysmenorrhea according to 100-mm VAS scores in all the reviewed studies using this scale. With regards to noncyclic pelvic pain and dyspareunia, the reviewers also reported clinically significant reductions. OCP treatment further resulted in improvements in QoL in most studies that measured this outcome (Jensen*, et al.*, 2018)

A Cochrane review by Brown *et al*, based on 5 RCTs comparing combined OCP with placebo (2 RCTs) and other medical treatments (3 RCTs) (Brown*, et al.*, 2018). From the trials comparing OCP with placebo, the review concluded that OCP was associated with improvements in self-reported pain (dysmenorrhea), cyclical non-menstrual pain, dyspareunia and dyschezia. From the trials comparing OCP with another medical treatment, data suitable for meta-analysis were only available from one trial that compared the OCP with goserelin (Vercellini*, et al.*, 1993). There was no clear evidence of a difference between groups for dysmenorrhea pain reduction or non-menstrual pain reduction.

II.2.a.2. Continuous vs cyclic use

Continuous use of the OCP and the associated achievement of amenorrhea, rather than standard cyclic use, has been suggested as an effective treatment for endometriosis-associated dysmenorrhea (Vercellini*, et al.*, 2003). Additionally, it was hypothesised that continuous treatment with OCP may homogenise the hormonal milieu and increase the efficiency of therapy (Vercellini*, et al.*, 2003).

Efficacy

A systematic review and meta-analysis by Muzii and colleagues compared continuous versus cyclic OCP use for the treatment of endometriosis-associated pain and reported that the continuous regimen appears to be more efficacious with regards to dysmenorrhea recurrence (RR 0.24; 95%CI 0.06-0.91) (Muzii*, et al.*, 2016). Nonsignificant differences between continuous and cyclic OCP use were reported for chronic pelvic pain and dyspareunia, and a trend toward lower cyst recurrence rates for a continuous OCP (RR 0.54; 95%CI 0.28 to 1.05).

Safety

In a review on OCP use, continuous treatment did not seem to affect coagulation, metabolism, or bone metabolism and bone mineral density more than conventionally taken OCPs (Hee*, et al.*, 2013). The review did not find any comparative studies on the risk of arterial complications with conventional OCP use vs. continuous OCP use.

II.2.a.3. Mode of administration

In the review of Grandi *et al*, studies reporting on the efficacy of the vaginal ring and transdermal patch were summarised (Grandi*, et al.*, 2019). The review reported two studies. A patient preference trial

showed that continuous 48-week treatment with a vaginal ring (ethinylestradiol (EE) 15 mg + etonogestrel 120 mg/d) was more effective than a transdermal patch (EE 20 mg + norelgestromin 150 mg/d) (Vercellini, *et al.*, 2010). The second study compared desogestrel-only contraceptive pill versus sequential contraceptive vaginal ring in the treatment of rectovaginal endometriosis infiltrating the rectum. At 48 weeks of follow-up, women using the desogestrel-only contraceptive pill group reported a significantly higher rate of treatment satisfaction and they were significantly more satisfied with changes in gastrointestinal symptoms. No difference was reported regarding the reduction in nodule volume, the rate of withdrawal after the completion of the study and the rate of women who decided to undergo surgery (Leone Roberti Maggiore, *et al.*, 2014)

Recommendations (13-14)

It is recommended to prescribe women a combined hormonal contraceptive (oral, vaginal ring or transdermal) to reduce endometriosis-associated dyspareunia, dysmenorrhea, and non-menstrual pain.	⊕⊕◯◯

Women suffering from endometriosis-associated dysmenorrhea can be offered the continuous use of a combined hormonal contraceptive pill.	⊕⊕◯◯

Justification

The Cochrane review on OCP for endometriosis-associated pain reported the OCP to be more effective than placebo for treatment of endometriosis-associated pain (Brown, *et al.*, 2018). Another review, including both RCTs and observational studies, reported clinically important and statistically significant reductions in endometriosis-related pain with OCP treatment (Jensen, *et al.*, 2018). As OCP is cost-effective (cheap), considered safe and often required for contraception, the GDG formulated a strong recommendation for the use of the OCP. Only 2 patient preference trials provided data on the comparison of different modes of administration (OCP, vaginal contraceptive ring, transdermal patch). With sparse data, preference one mode of administration could not be recommended over another.
In the comparison of continuous versus cyclic OCP use, the data for efficacy are deduced from few small studies, although summarised in a meta-analysis. Data show that continuous OCP use may be superior for dysmenorrhea recurrence (Muzii, *et al.*, 2016). A review by Hee *et al.* reported no difference in the safety profile of both regimens (Hee, *et al.*, 2013). As such, continuous OCP use can be offered (weak recommendation), for instance when patients with endometriosis prefer a regimen that induces amenorrhea. The occurrence of breakthrough bleeding and possible consequential adaptations to the medical treatment should be discussed with the patient.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question II.2).

II.2.b. Progestogens (including progestogen-only contraceptives) and anti-progestogens.

II.2.b.1 Efficacy

The Cochrane review of Brown *et al.* is the most recent Cochrane review reporting on the effectiveness of progestogens (including progestogen-only contraceptives) and anti-progestogens in the treatment of endometriosis-associated pain (Brown, *et al.*, 2012). Interventions included in the review are depot medroxyprogesterone acetate, cytoproterone acetate, medroxyprogesterone acetate, norethindrone/norethisterone acetate, desogestrel (both commonly also prescribed as progestogen-

only contraceptives) and dienogest. Gestrinone was the only anti-progestogen (i.e., a substance that prevents cells from making or using progesterone) included. The conclusion from this literature review is that both continuous progestogens and continuous gestrinone are effective therapies for the treatment of painful symptoms associated with endometriosis. There was no overall evidence of a benefit of one oral progestogen over another. However, this conclusion must be treated with caution due to the paucity of data and lack of placebo-controlled studies.

Only 1 more recent review was found evaluating the efficacy of progestogens (dienogest) (Andres Mde*, et al.*, 2015). For the efficacy, it referred to the same studies already included in the Cochrane review (Brown*, et al.*, 2012). The majority of the other 'progestogen' studies published over the last few years have focused mainly on dienogest but are limited to small retrospective and prospective studies.

II.2.b.2. Safety

The Cochrane review of Brown included both efficacy and safety. Adverse effects reported with dydrogesterone use included severe headaches and cycle irregularity, while acne and oedema were reported with medroxyprogesterone use. Patients receiving depot progestogens had significantly more injection site reactions (OR 20.64, 95%CI 1.19 to 358.23) than with other treatments. They also experienced more bloating (OR 4.39, 95%CI 1.71 to 11.30), intermenstrual bleeding (OR 20.56, 95%CI 6.44 to 65.56), weight gain (OR 2.58, 95%CI 1.03 to 6.46), amenorrhea (OR 21.18, 95%CI 1.18 to 380.9), and nausea (OR 3.86, 95%CI 1.12, 13.26) compared with other treatments. Amenorrhea (OR 4.95, 95%CI 2.88 to 8.52) and bleeding (OR 4.69, 95%CI 2.47 to 8.90) were reported more frequently with the use of oral progestogen. Hirsutism and seborrhoea (greasy skin) have been reported with the use of anti-progestogens (gestrinone).

The review of Dragoman *et al.* summarised the data on the safety of subcutaneously (SC) administered depot medroxyprogesterone acetate (DMPA) (Dragoman and Gaffield, 2016). The review included 14 studies: 10 on DMPA users of varying age or with obesity, endometriosis, or HIV and four on the safety of DMPA-SC and DMPA-IM in healthy women. The review reported no differences in bone mineral density among adult DMPA-SC and DMPA-IM users at two years of follow-up (based on one trial). Women with endometriosis using DMPA-SC over six months had minimal decreases in bone mineral density, weight gain, few serious adverse events and experienced improved pain symptoms.

II.2.b.3. Long term use

In the review by Andres 2015, two studies were included reporting on the longer-term use of dienogest. In an extension study, following up on the study of Strowitzki *et al*, patients were assigned to treatment with dienogest 2mg/day for 36 weeks (n=17) or 52 weeks (n=135) (Petraglia*, et al.*, 2012, Strowitzki*, et al.*, 2010). The study reported an improvement in pain for both the group previously treated with dienogest and for the group previously treated with placebo (from 40.73 ± 21.14 to 13.49 ± 14.14mm versus 27.89 ± 20.24 to 9.72 ± 7.44mm, respectively). Adverse effects were reported in 27 of 168 women, including breast discomfort (n=7; 4.2%), nausea (n=5; 3.0%) and irritability (n=4; 2.4%).

In another longer-term study, the use of 52 weeks of dienogest (2mg/day) was evaluated (Momoeda*, et al.*, 2009). A reduction in VAS score for pelvic pain was noted after 24 and 52 weeks of treatment (-22.5 ± 32.1 and -28.4 ± 29.9mm, respectively). All patients experienced some side effects, such as vaginal bleeding (71.9%), headache (18.5 %), constipation (10.4%), nausea (9.6%) and hot flushes (8.9%). The percentage of patients with amenorrhea was 7.4% within 5–8 weeks and 40.5% at 49–52 weeks of treatment.

II.2.b.4. Mode of administration (intrauterine system/subdermal implant)

A systematic review of RCTs comparing the levonorgestrel-releasing intrauterine system (LNG-IUS) with GnRH agonist included five trials with a total of 255 women (Lan*, et al.*, 2013). In three of the trials

reporting on VAS scores, LNG-IUS was found to reduce pain scores, with no difference compared to GnRH agonist (weighted mean difference [WMD] 0.03: 95%CI -0.53 to 0.59). In a fourth trial, LNG-IUS treatment decreased ASRM staging scores and improved HRQoL similar to GnRH-agonist. One study reported reduced cardiovascular risk factors (low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC)) compared to GnRH-agonist. Irregular bleeding, simple ovarian cysts and one-sided lower abdominal pain occurred more commonly in the LNG-IUS group while vasomotor symptoms and amenorrhea were observed more frequently in the GnRH agonist group.
A recent RCT randomised 103 women with endometriosis-associated chronic pelvic pain and/or dysmenorrhea to an etonogestrel-releasing subdermal implant (ENG) or a 52-mg levonorgestrel-releasing intrauterine system (Margatho*, et al.*, 2020). The study reported that both the ENG implant and the LNG-IUS significantly reduced endometriosis-related pain, dysmenorrhea, and chronic pelvic pain. However, the study reported a high rate of discontinuation and loss to follow-up at 24 months in both arms: 65% for the ENG implant and 63% for the 52-mg LNG-IUS.

II.2.b.5. Danazol

Danazol, a synthetic steroid derived from ethinyl testosterone, was used for many decades for the treatment of endometriosis-associated symptoms and was the standard control medication in many clinical drug trials. It has a high affinity to the androgen receptor and moderate affinity to progesterone and glucocorticoid receptors which is the cause of unwanted side effects. The GDG strongly believes that oral danazol should not be used unless no other medical therapy is available, due to its severe side effects (acne, oedema, vaginal spotting, weight gain, muscle cramps, deepening of voice, increase in facial hair). For this reason, danazol is no longer described as a medical treatment for endometriosis-associated pain in the current guideline. Whether transvaginal application of danazol has a more favourable side effect profile whilst keeping its clinical efficacy as suggested in smaller studies, would need to be assessed in larger RCTs in the future (Godin and Marcoux, 2015).

Recommendations (15-17)

It is recommended to prescribe women progestogens to reduce endometriosis-associated pain.	⊕⊕◯◯
The GDG recommends that clinicians take the different side effect profiles of progestogens into account when prescribing them.	GPP
It is recommended to prescribe women a levonorgestrel-releasing intrauterine system or an etonogestrel-releasing subdermal implant to reduce endometriosis-associated pain.	⊕⊕⊕◯

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 recommendations.

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.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question II.2)

II.2.c. GnRH agonists

II.2.c.1 Efficacy

A Cochrane review published in 2010 compared GnRH agonist at different doses, regimens, and routes of administration, with danazol, with intrauterine progestogens, and with placebo/no treatment for relieving endometriosis-associated pain symptoms (Brown*, et al.*, 2010). The results suggest that a GnRH agonist is more effective than placebo but inferior to the levonorgestrel-releasing intrauterine system or oral danazol. No difference in effectiveness exists whether GnRH agonists are administered intramuscularly, subcutaneously or intranasally.

A RCT by Tang and colleagues randomised 50 women with stage III-IV endometriosis to either 3.75mg (full dose) or 1.88mg (half dose) of GnRH agonist (Leuprorelin) (Tang*, et al.*, 2017). Surgery combined with the 3.75-mg GnRH agonist or with the 1.88-mg GnRH agonist relieved the degree of dysmenorrhea, although one case of light dysmenorrhea occurred in each group. There was no significant difference between treatments after resumption of menstruation.

II.2.c.2. Safety

The review by Brown *et al.* found a poor side effect profile for GnRH agonists in all studies (Brown*, et al.*, 2010). Five of the most reported side effects were vaginal dryness, hot flushes, headaches, weight gain and acne. In studies comparing different routes of administration, hot flushes, vaginal dryness, headaches, and decreased libido were reported, but there was no difference between intramuscular, subcutaneous, or intranasal administration.

In the RCT by Tang and colleagues, the bone mineral density (BMD) was decreased in both groups (3.75 mg and 1.88 mg leuprorelin) at 20 weeks after treatment, but the degree of loss of BMD was significantly higher in the full dose group (5.6% vs 1.2%) (Tang*, et al.*, 2017).

II.2.c.3. Add-back therapy.

Reduction of bone mineral density is one of the undesirable effects of long-term GnRH-agonist treatment. There are many combinations of add-back regimens that are effective in preventing bone loss when administered with GnRH agonists. These add-back regimens include progestin monotherapy such as norethisterone/norethindrone acetate (NETA), estrogen-progestin combinations, selective estrogen receptor modulators, bisphosphonates, tibolone, and testosterone (Sauerbrun-Cutler and Alvero, 2019).

A meta-analysis of Wu *et al.* included 13 RCTs comparing efficacy of GnRH agonist or GnRH agonist plus "add-back" therapy for endometriosis (Wu*, et al.*, 2014). Lumbar spine BMD after treatment (12 RCTs; mean difference MD -0.03; 95%CI -0.05 to -0.02) and at 6 months of follow-up (MD -0.02; 95%CI -0.03 to -0.01; 6 RCTs) were superior with GnRH agonist + add-back therapy than with GnRH agonist alone. Femoral neck BMD after treatment was assessed in 3 trials, but there were no significant differences between GnRH agonist + add-back therapy and GnRH agonist alone (MD -0.01; 95%CI -0.02 to 0.01; 3 RCTs). There was no statistically significant difference in dysmenorrhea scores (MD – 0.27; 95%CI -0.93

to 0.39; 5 RCTs) or dyspareunia scores after treatment (MD 0.05; 95%CI -0.37 to 0.47; 4 RCTs) when comparing GnRH agonist and add-back therapy with GnRH agonist alone (Wu*, et al.*, 2014).

Recommendations (18-20)

It is recommended to prescribe women GnRH agonists to reduce endometriosis-associated pain, although evidence is limited regarding dosage or duration of treatment.	⊕⊕◯◯
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.	GPP
Clinicians should consider prescribing combined hormonal add-back therapy alongside GnRH agonist therapy to prevent bone loss and hypoestrogenic symptoms.	⊕⊕⊕◯

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, summarised in a systematic review (Wu*, et al.*, 2014), 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).

More information is covered in chapter V.2 Treatment for endometriosis in adolescents.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question II.2)

II.2.d. GnRH antagonists

GnRH antagonists have been added to this update of the medical treatment options for endometriosis.

Data on efficacy can be deduced from a report on the two similar multicentre, double-blind, randomised, placebo-controlled, phase three trials of six-month treatment with oral elagolix at two doses in women with moderate or severe endometriosis-associated pain. The two primary efficacy endpoints were the proportion of women who had a clinical response with respect to dysmenorrhea and the proportion who had a clinical response with respect to non-menstrual pelvic pain at three months (measured as a clinically meaningful reduction in the pain score (and a decreased or stable use of rescue analgesic agents). The proportion of women who met the clinical response criteria for each of the two primary end points was significantly greater among women who received each elagolix dose

(46.4% in the lower dose group, 75.8% in the higher dose group) than among those who received placebo (19.6%). The reductions in dysmenorrhea and non-menstrual pelvic pain were apparent at 1 month and were sustained at 6 months. More than 70% of women in each trial group reported at least one adverse event, with a significant difference in frequency between those receiving the higher dose of elagolix and those receiving placebo. The most frequently reported adverse events were hot flushes, headache, and nausea (Taylor, *et al.*, 2017).

Two smaller RCTs support the efficacy of other GnRH antagonists (Donnez, *et al.*, 2020, Osuga, *et al.*, 2020). Compared with placebo, oral doses of ≥75mg of linzagolix resulted in a significantly greater reduction in overall pelvic pain at 12 weeks (34.5%, 61.5%, 56.4%, and 56.3% for placebo, 75, 100, and 200mg, respectively) (Donnez, *et al.*, 2020). Similarly, oral administration of relugolix at 10, 20 and 40mg alleviated endometriosis-associated pain in a dose-response manner and was generally well tolerated (Osuga, *et al.*, 2020).

Recommendation (21-22)

It can be considered to prescribe women GnRH antagonists to reduce endometriosis-associated pain, although evidence is limited regarding dosage or duration of treatment.	⊕⊕⊕○

The GDG recommends that GnRH antagonists are prescribed as second line (for example if hormonal contraceptives or progestogens have been ineffective) due to their side-effect profile.	GPP

Justification

Emerging evidence from RCTs on oral GnRH antagonists (elagolix, relugolix and linzagolix) suggest that they are effective in the relief of endometriosis-associated painThe evidence remains limited regarding dosage or duration of treatment, the need for add-back therapy and no specific GnRH antagonist can be recommended over another in relieving endometriosis-associated pain. Hence, a weak recommendation was formulated. Like, GnRH agonists, there is evidence of considerable side effects with these drugs (including potential impact on bone density), and they should be discussed with the patient when offering this treatment.

Similar as for GnRH agonists, the GDG recommends that in young women and adolescents, GnRH antagonist should be used after careful consideration and discussion with a practitioner in a secondary or tertiary care setting, considering potential side effects and long-term health risks (e.g., bone health).

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question II.2)

II.2.e. Aromatase inhibitors

II.2.e.1 Efficacy

The most recent systematic review available on aromatase inhibitors for the treatment of endometriosis-associated pain was published in 2011. Ferrero *et al.* included 7 studies, 2 of which were from the authors' own group (Ferrero, *et al.*, 2011). The minimum number of individuals in each trial was 10. The review found that treatment with oral letrozole plus norethisterone acetate (NEA) or desogestrel, or anastrozole as vaginal suppository (250µg daily) or orally (1mg daily) in combination with OCP resulted in a significant decrease of endometriosis-associated pain in premenopausal women. The same appears to be true for letrozole plus either NEA or triptorelin, although letrozole plus

triptorelin resulted in more side effects than NEA. The authors concluded that aromatase inhibitors should be investigated long-term to see if they are superior to currently available endocrine therapies in terms of improvement of pain, adverse effects, and patient satisfaction.

One RCT and one prospective cohort study were published after the inclusion deadline for the review of Ferrero and colleagues. The RCT included 51 women with pelvic endometriosis and endometriotic pain (dyspareunia, dysmenorrhea, pelvic pain) score of 5 or more (for at least one of these endometriotic pain), after laparoscopic diagnosis and conservative laparoscopic surgery. Patients were treated for 4 months with letrozole plus OCP (n=25) or only OCP (n=26) (Almassinokiani*, et al.*, 2014). The study showed a decline in VAS score, the score of dyspareunia, dysmenorrhea, and pelvic pain, but reported no difference between the groups.

The prospective cohort study assessed the impact of 3 months aromatase inhibition (letrozole 5mg/d) together with progestin add-back on ovarian endometrioma size and symptoms (Agarwal and Foster, 2015). The study compared the size of 14 endometriomas in 8 consecutive women before and after treatment. The mean endometrioma diameter decreased 50% from 4.6±1.6 cm to 2.3±1.6 cm (mean ± SD). The study also reported a reduction in patient reported symptom endpoints of the Biberoglu and Behrman scale, with mean dyspareunia score decreasing from 2 to 0 and mean dyspareunia and non-menstrual pelvic pain scores decreasing from 1 to 0.

II.2.e.2. Safety and availability

We acknowledge that aromatase inhibitors are not available (even off-label) in some countries. The most common third-generation aromatase inhibitors letrozole and anastrozole are reversible inhibitors of the enzyme aromatase, competing with androgens for aromatase binding sites. The side effects are mostly hypoestrogenic in nature and include vaginal dryness, hot flushes, and diminished bone mineral density. Due to the reduction of estrogen-driven negative feedback at the hypothalamic pituitary axis, aromatase inhibitors are used for ovulation induction. Therefore, pregnancies with higher rates of multiples are a potential complication of this treatment. Earlier reports of increased cardiovascular risks have not been substantiated.

Recommendation (23)

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 antagonists.	⊕⊕◯◯

Justification

The evidence consists of a systematic review from 2011, including mostly non-randomised 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 (strong recommendation).

Medical treatments adjunct to surgery to improve surgical outcomes, or to prevent recurrence are described in sections II.4 and chapter IV, respectively.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question II.2).

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II.3. Surgical treatment

Surgical treatment to eliminate endometriotic lesions and divide adhesions has long been an important part of the management of endometriosis. Historically, surgical approaches were achieved at open surgery, but in recent decades, laparoscopy has dominated. Elimination of endometriosis may be achieved by excision, diathermy, or ablation/vaporisation. Division of adhesions aims to restore pelvic anatomy. In addition, some clinicians use interruption of pelvic nerve pathways with the intention of improving pain control.

The current section focuses on the efficacy and safety of surgery for management of pain in women with endometriosis. Technical guidance on surgical techniques for surgery in endometriosis has been previously published by a working group of ESGE, ESHRE and WES (Working group of ESGE ESHRE and WES*, et al.*, 2020a, b, Working group of ESGE ESHRE and WES*, et al.*, 2017a, Working group of ESGE ESHRE and WES*, et al.*, 2017b).

PICO QUESTION: IS SURGERY EFFECTIVE FOR TREATMENT OF PAIN ASSOCIATED WITH ENDOMETRIOSIS?

II.3.a. Surgery versus diagnostic laparoscopy/medical treatment

The efficacy of laparoscopic treatment of endometriosis has been compared against diagnostic laparoscopy or medical treatment. A recent Cochrane review analysed only 2 of the published RCTs (Abbott*, et al.*, 2004, Jarrell*, et al.*, 2005) that compared surgical treatment of endometriosis with diagnostic laparoscopy only (Bafort*, et al.*, 2020a). The reviewers concluded that they were uncertain of the effect of laparoscopic surgery on overall pain score and quality of life due to low or very low quality of these studies. In the included trials the method of treatment was either excision, coagulation, or CO_2 laser vaporisation of endometriotic lesions. Another study included and analysed in the previous version of the Cochrane review by Sutton *et al.* (n=63), included laparoscopic uterosacral nerve ablation (LUNA) in addition to CO_2 laser vaporisation of endometriotic lesions and adhesiolysis in the treatment arm (Sutton*, et al.*, 1994). They found that laparoscopic surgery was better than diagnostic laparoscopy in reducing overall pain at 6 months. Abbott *et al.* randomised 39 women with endometriosis to immediate excision or diagnostic laparoscopy (or delayed excision) groups and found that a significantly greater number of women in the immediate excision reported overall pain improvement at 6 months (Abbott*, et al.*, 2004). Jarrell *et al.* (n=16, excision vs diagnostic laparoscopy) showed again that surgery was more effective than diagnostic laparoscopy in reducing overall pain at 6 months (mean difference [MD] 0.90; 95%CI 0.31 to 1.49) and 12 months (MD 1.65; 95%CI 1.11 to 2.19) (Jarrell*, et al.*, 2005). It is worth noting that there were relatively few patients with stage III/IV endometriosis in these trials. The studies included in this review reported no major complications. When different types of pain were considered, including pelvic pain, dysmenorrhea, dyspareunia, and dyschezia, there was insufficient evidence to determine which pain type responded best to laparoscopic surgery (Bafort*, et al.*, 2020a).

II.3.a.1 Impact of surgery on QoL

A recent systematic review and meta-analysis reported on the impact of surgery for endometriosis on major domains of QoL as assessed by SF-36, SF-12, EHP-30 or EQ-5D (Arcoverde*, et al.*, 2019). Of the 38 included studies 8 including 983 patients with all types of endometriosis with follow-up of 3-37 months analysed the effect of surgery. Three studies with a total of 269 patients were meta-analysed for Mental Component Score (MCS) and Physical Component Score (PCS), surgery significantly

improved MCS (OR 0.21, 95%CI 0.05-0.38), but not PCS (Abbott, *et al.*, 2004, Abbott, *et al.*, 2003, Soto, *et al.*, 2017). A fourth RCT by Vercellini *et al.* with 180 patients showed significant improvement of health related QoL, psychiatric profile and sexual satisfaction scores (Vercellini, *et al.*, 2003). Two studies using EQ-5D including 443 patients showed improvements in all domains, except anxiety (M F, *et al.*, 2017, Roman, 2010). One study looked at benefit of laparoscopic surgery in 161 women with minimal endometriosis and found significant improvement in both PCS (49.4 ± 9.8 vs 52.3 ± 7.8; p=0.002) and MCS (40.6 ± 12.21 vs 45.0 ± 11.3; p<0.001), but only 16% of women had a 5 point or more improvement in their scores (Valentin, *et al.*, 2017).

Franck *et al*. carried out a systematic review of the studies which reported quality of sexual life (QoSL) before and after laparoscopic surgery for endometriosis (Franck, *et al.*, 2018). They could not perform a meta-analysis due to heterogeneity between the 12 included studies. They did however note that six of the seven validated questionnaires used in the 12 studies identified improvements in sexual function following laparoscopic surgery for endometriosis regardless of location, severity of the disease and hormone treatment.

Recommendations (24)

It is recommended to offer surgery as one of the options to reduce endometriosis-associated pain.	⊕⊕◯◯

Justification

Although summarised in a Cochrane review, there are only a few small trials comparing pain outcomes after diagnostic laparoscopy and laparoscopic interventions, and meta-analysis could not be performed. This limits the group to make any valid conclusions on the benefit of surgery for the treatment of endometriosis-associated pain.

Before and after studies assessing the effect of surgical intervention on pain and quality of life have been summarised in another review, reporting that surgery for endometriosis resulted in overall improvement in most health domains of health related QoL, with the greatest improvement found in the Bodily Pain domain (Arcoverde, *et al.*, 2019). A similar conclusion was reported for quality of sexual life (Franck, *et al.*, 2018). It must be considered that surgical trials mostly use a follow up of 6 to 12 months, although some studies followed up patients up to 3 years. Surgery for endometriosis is considered a relatively safe procedure, based on studies showing low numbers of (severe) complications (Bafort, *et al.*, 2020b, Byrne, *et al.*, 2018b, Chapron, *et al.*, 1998). Considering these data, a strong recommendation was formulated stating that clinicians should offer surgical treatment as one of the options to relief endometriosis-associated pain.

Laparoscopy is usually associated with less pain, shorter hospital stay, quicker recovery and better cosmesis, hence it is usually preferred to open surgery. If the relevant experience with laparoscopy is not available, the patient should be referred to a centre of expertise.

Specific data and recommendations on surgery for subtypes of endometriosis are discussed below.

Research recommendation (R6)

Research should investigate the effect of surgery on pain and QoL parameters in different subtypes, preferably via longitudinal population studies.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question II.3).

II.3.b. Ablation versus excision of endometriosis

A systematic review and meta-analysis (Pundir, *et al.*, 2017) identified three RCTs (Barton-Smith, 2010, Healey, *et al.*, 2010, Wright, *et al.*, 2005) comparing excision with ablation of endometriosis. The study by Wright *et al.* was not included in the meta-analysis because of incomplete data but showed that excision and ablation equally improved pelvic pain associated with mild endometriosis (Wright, *et al.*, 2005). Meta-analysis of the other two RCTs showed that laparoscopic excision was significantly superior to ablation in reducing symptoms of EHP-30 core pain score, dyschezia, and chronic pelvic pain (Pundir, *et al.*, 2017). There was also a trend in reduction of dysmenorrhea and dyspareunia scores after excision compared to ablation, but this did not reach statistical significance. One of these three RCTs later published their 5 year follow up data and it showed that excision was better than ablation in treating deep dyspareunia (Healey, *et al.*, 2014).

Another systematic review and meta-analysis was published recently, aiming to update the literature on the surgical management of minimal to mild endometriosis (Burks, *et al.*, 2021). The study identified four RCTs (Healey, *et al.*, 2010, Radosa, *et al.*, 2010, Riley, *et al.*, 2019, Wright, *et al.*, 2005), out of which three were compared and analysed for meta-analysis (Healey, *et al.*, 2010, Riley, *et al.*, 2019, Wright, *et al.*, 2005). The review examined mean reduction of visual analogue scale (VAS) score from baseline to 12 months postoperative, or mean VAS score at 12 months postoperative for dysmenorrhea, dyschezia, dyspareunia and concluded that there are no significant differences between excision and ablation groups with regards to improving pain measured with the above parameters.

Recommendation (25)

When surgery is performed, clinicians may consider excision instead of ablation of endometriosis to reduce endometriosis-associated pain.	⊕⊕◯◯

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.

II.3.c. Superficial peritoneal endometriosis

Some consider superficial peritoneal endometriosis (SPE) as a separate entity than ovarian endometriomas and deep endometriosis. However, others argue that they are frequently found together, and are likely to be different forms of the same condition.

There are no trials specifically studying the effect of surgery for SPE on pain symptoms. Some studies included only women with ASRM stage I and II and majority of these may have SPE. However, ASRM I and II disease may also have women with ovarian endometriomas smaller than 1cm or deep endometriosis, hence it would be impossible to generalise the results of these studies to women with SPE only.

Research recommendation (R7)

The GDG recommends sufficiently powered prospective, randomised and ideally blinded studies to unequivocally determine whether surgical treatment of superficial peritoneal endometriosis improves short and long-term clinical outcomes such as a reduction in pain symptoms and improvement in quality of life.

II.3.d. Surgical interruption of pelvic nerve pathways

The effectiveness of surgical interruption of pelvic nerve pathways in primary and secondary dysmenorrhea was analysed in a Cochrane review that included six RCTs on women with endometriosis (Proctor, *et al.*, 2005). Three of these RCTs evaluated the effect of laparoscopic uterosacral nerve ablation (LUNA) together with conservative laparoscopic surgery for endometriosis (Johnson, *et al.*, 2004, Sutton, *et al.*, 2001, Vercellini, *et al.*, 2003); the other three (Candiani, *et al.*, 1992, Tjaden, *et al.*, 1990, Zullo, *et al.*, 2003) studied the effects of presacral neurectomy (PSN) (two at laparotomy, one at laparoscopy) in addition to conservative (organ or fertility preserving) surgery for endometriosis. The RCTs on LUNA showed that this technique did not offer any additional benefit as an adjunct to conservative surgery one year after surgery. The assessment at 6 months did not show any benefit either, but this included one additional trial studying patients who had fibroids. There were significant benefits of PSN at 6 months (1 RCT) and 12 months (2 RCTs). One of the RCTs included in the Cochrane review above reported 24-month follow-up results of PSN in addition to laparoscopic surgery for endometriosis compared to laparoscopic surgery only for the treatment of severe dysmenorrhea, dyspareunia, and pelvic pain due to endometriosis (Zullo, *et al.*, 2004). Frequency and severity of dysmenorrhea, dyspareunia, and chronic pelvic pain; and quality of life were evaluated. PSN group had better improvement of dysmenorrhea, dyspareunia, pelvic pain, and quality of life compared to laparoscopic surgery only.

However, PSN is associated with increased risk of adverse effects such as bleeding, constipation, urinary urgency and painless first stage of labour (Proctor, *et al.*, 2005). The data suggest that the effect of PSN may be specific to midline pain only.

A more recent systematic review and meta-analysis of 7 controlled studies -including the 3 RCTs summarised in Proctor *et al.* - reported on treatment failure and complications. They concluded that whilst PSN may be beneficial in selected patients with midline pain, based on a lower risk of treatment failure in these patients (RR 0.43; 95%CI 0.30 to 0.60), the published data come from older and low-quality studies (Miller, *et al.*, 2020). As endometriosis surgery improved in the recent decades, the place of PSN needs to be confirmed in patients who undergo radical excision of deep endometriosis.

Conclusion

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.

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 labour.

II.3.e. Surgery for ovarian endometrioma

To our knowledge, there are no RCTs comparing cystectomy versus no treatment in women with endometrioma and measuring the effect on pain symptoms.

II.3.e.1 Surgical technique

A Cochrane review by Hart and co-workers (Hart, *et al.*, 2008) reviewed two RCTs comparing laparoscopic excision of ovarian endometriotic cysts (3 cm or larger) to drainage and coagulation by bipolar diathermy (Alborzi, *et al.*, 2004, Beretta, *et al.*, 1998). Both studies demonstrated lower recurrence of dysmenorrhea and dyspareunia after cystectomy compared to drainage and coagulation

only. There were fewer cyst recurrences with the excisional approach. Need for further surgery and recurrence of non-menstrual pain were less likely after cystectomy (Hart, *et al.*, 2008).

An additional RCT, published after the Cochrane review, randomised 90 women to cystectomy or CO_2 laser vaporisation. The trial showed that recurrence of cysts was more common at 12 months, but not at 60 months, after CO_2 laser vaporisation, and that the time to recurrence was shorter, compared to cystectomy (Carmona, *et al.*, 2011). In a retrospective study of 125 women, Candiani *et al.* showed that recurrence rates after an average of 29-month follow up were similar after CO_2 fibre laser vaporisation and cystectomy for endometriomas (Candiani, *et al.*, 2020). The most important indicator for recurrence was endometriomas larger than 5 cm (OR 2.21; 95%CI 1.19 to 3.32).

A small multicentre RCT (n=51) compared stripping and combined excision/ablation techniques for the treatment of bilateral ovarian endometriomas larger than 3 cm (Muzii, *et al.*, 2016). Similar recurrence rates were observed for the two techniques at 6-month follow-up. Recurrence rates were 5.9% for the stripping technique versus 2.0% for the combined technique (OR 3.00; 95%CI 0.24 to 157.5).

A recent RCT compared four groups of women with endometrioma who underwent drainage (with bipolar coagulation) or cystectomy with or without oxidised regenerated cellulose (ORC, Surgicel) for haemostasis to study effect on ovarian reserve and endometrioma recurrence rates (Shaltout, *et al.*, 2019). They found that use of ORC reduced recurrence rates with the lowest recurrences seen in the cystectomy + ORC group followed by drainage + ORC.

Two RCTs looked at direct stripping of endometrioma at the original adhesion site compared to circular excision at the initial adhesion site followed by stripping (Mossa, *et al.*, 2010, Muzii, *et al.*, 2005). Muzii *et al.* found that it was easier to remove the cyst with the circular excision technique but duration of operation, intraoperative complications and postoperative endometrioma recurrence rates were similar (Muzii, *et al.*, 2005). Mossa *et al.* showed that initial circular excision followed by stripping was quicker, had shorter haemostasis times and had higher complete excision rates (Mossa, *et al.*, 2010). However, the recurrence rates were not different. The average cyst size was bigger in the direct stripping group and blinding was unclear, hence the results should be interpreted with caution.

A prospective cohort study was conducted, and postoperative follow-up visits were scheduled every 3 months following complete laparoscopic excision of endometriosis including endometriomas to identify pain and/or endometrioma recurrence for a minimum of 3 years (Porpora, *et al.*, 2010). Dysmenorrhea, dyspareunia, and chronic pelvic pain recurred in 14.5%, 6%, and 5.4% of women, respectively. Ovarian endometrioma recurred in 9.6% of cases.

The risk of ovarian failure after bilateral ovarian endometrioma removal is reported to be 2.4% (Busacca, *et al.*, 2006). The impact of ovarian surgery on ovarian reserve has been assessed as a secondary outcome in several of the above-mentioned studies. In studies comparing AFC and ovarian volume at 6-month follow-up, AFC was similar, but ovarian volume was lower in ovaries where endometrioma were treated with a combined excision/ablation technique compared to stripping (Muzii, *et al.*, 2016). Shaltout and colleagues reported a similar impact of drainage or cystectomy (with or with ORC) on ovarian reserve, but also reported that drainage + ORC has the least impact on AMH, and that drainage had a significantly higher impact of AFC compared to cystectomy + ORC (Shaltout, *et al.*, 2019). A prospective study showed that surgery for recurrent endometriomas is more harmful to healthy ovarian tissue and ovarian reserve than first surgery as demonstrated by removal of larger ovarian tissue at histology and a trend towards lower AFC at follow up (Muzii, *et al.*, 2015). A recent systematic review and meta-analysis confirmed that cystectomy, particularly for bilateral endometriomas, has a deleterious and sustained effect on ovarian reserve (Younis, *et al.*, 2019).

Recommendations (26-28)

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.	⊕⊕◯◯

When performing surgery in women with ovarian endometrioma, clinicians can consider both cystectomy and CO_2 laser vaporisation, as both techniques appear to have similar recurrence rates beyond the first year after surgery. Early post-surgical recurrence rates may be lower after cystectomy.	⊕◯◯◯

When performing surgery for ovarian endometrioma, specific caution should be used to minimise ovarian damage.	⊕◯◯◯

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 CO_2 laser vaporisation.

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 CO_2 laser vaporisation, one RCT and one retrospective study were available (Candiani*, et al.*, 2020, Carmona*, et al.*, 2011), 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. A weak recommendation was formulated.

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.

Information on diagnosis of deep endometriosis is covered in chapter I. Treatment for asymptomatic endometriosis is covered in chapter VIII.

II.3.f. Surgery for deep endometriosis

Deep endometriosis (DE) extends beneath the peritoneum and may affect the uterosacral ligaments, pelvic side walls, rectovaginal septum, vagina, bowel, bladder, or ureter. Excision of these nodules is usually performed when surgical treatment is chosen. Colorectal involvement is not rare with deep endometriosis, Deep endometriosis involving the bowel has been reported in 5-12% of women affected by endometriosis (Wills*, et al.*, 2008). The term 'bowel endometriosis' is used when endometrial-like glands and stroma infiltrate the wall of the gastrointestinal tract (Chapron*, et al.*, 2003). In case of bowel

infiltration, about 90% is localised on the sigmoid colon or the rectum. Other locations such as small bowel, appendix, and cecum are less frequent. Colorectal involvement could lead to change in bowel habits, such as constipation, diarrhoea, tenesmus, dyschezia, and rectal bleeding. These symptoms may vary depending on location and menstrual cycle (Kaufman*, et al.*, 2011). Therefore, precise diagnosis about presence, location, and extent of endometriosis is necessary to plan surgical treatment.

Treatment approaches for colorectal endometriosis include superficial shaving, discoid resection, and segmental resection of the bowel to remove the deep endometriosis nodules. Many case series have been published for these methods since the late 1980s.

A systematic review and meta-analysis by Arcoverde *et al.* analysed 8 articles which included 673 patients with deep endometriosis some including bowel endometriosis and 22 articles with 1580 patients with bowel endometriosis (Arcoverde*, et al.*, 2019). In the DE analysis, 3 articles (Angioni*, et al.*, 2015, Hong*, et al.*, 2014, Mabrouk*, et al.*, 2011) which used SF-36 and one study (Garry*, et al.*, 2000) which used SF-12 included 504 patients. Health-related Quality of Life (HRQoL) scores improved significantly in all domains, with the highest improvement in bodily pain. Two studies which used either EHP-30 (Vercellini*, et al.*, 2013) or EHP-5 (De la Hera-Lazaro*, et al.*, 2016) showed improvement in all domains.

A systematic review by Meuleman and co-workers looked at 49 papers on DE with colorectal involvement, including laparoscopic, laparotomic, transvaginal or combined approaches (Meuleman*, et al.*, 2011b). Although less than 50% of these pain-reporting studies had a median follow-up of more than 2 years, improvement of pain and digestive symptoms after surgery for colorectal endometriosis was reported. They found that pain and quality of life improvement was reported in most studies, the complication rate was 0-3% and the total recurrence rate (recurrence of symptoms or lesions) was 5-25%. However, they noted that most data were collected retrospectively, and study designs and reporting methods were variable. As it was impossible to make comparisons between different surgical techniques, a checklist was developed to standardise the reports of surgical trials for deep endometriosis (Meuleman*, et al.*, 2011b).

Another systematic review by De Cicco and co-workers included 34 articles on bowel resection for colorectal endometriosis (De Cicco*, et al.*, 2011). This review found excellent pain relief in most studies. They concluded that segmental bowel resection for deep endometriosis with colorectal involvement seemed to be a widely acceptable option. The decision to perform resection seemed to be based on preference rather than data; complication rates were similar to resections for other indications, and data on sexual dysfunction were lacking. They suggested that to permit meta-analysis, journals should adopt a standard way of reporting indications, surgery, outcome, size, and localisation of nodules. The common use of bowel resection may be due to bowel surgeons who are used to resections for cancer treatment (De Cicco*, et al.*, 2011).

More recently Arcoverde *et al.* analysed articles which reported HRQoL after surgery for bowel endometriosis (Arcoverde*, et al.*, 2019). Majority of these articles were published after the reviews by Meuleman *et al.* and De Cicco *et al.* (De Cicco*, et al.*, 2011, Meuleman*, et al.*, 2011b). In 12 studies which included 750 patients using SF-36 or SF-12 data, pooled results showed significant improvement of HRQoL in all 8 domains, MCS, PCS and total score (Arcoverde*, et al.*, 2019). Four studies which used endometriosis specific EHP-30 (Kent*, et al.*, 2016, Meuleman*, et al.*, 2011a, Meuleman*, et al.*, 2014) or EHP5 (Bailly*, et al.*, 2013) showed improvement in most domains studied. Studies which used specific urinary or gastrointestinal QoL questionnaires showed significant improvements as well.

The largest multicentre prospective case series to date published (BSGE Endometriosis Centres data, (Byrne*, et al.*, 2018a)) reported the 6, 12 and 24-month follow up outcome on nearly 5000 women undergoing laparoscopic excision of deep rectovaginal endometriosis. This showed significant

reductions in premenstrual, menstrual, and non-cyclical pelvic pain, deep dyspareunia, dyschezia, low back pain and bladder pain. In addition, there were significant reductions in voiding difficulty, bowel frequency, urgency, incomplete emptying, constipation and passing blood. These reductions were maintained at 2 years, except for voiding difficulty. Global quality of life significantly improved from a median retreatment score of 55/100 to 80/100 at 6 months. There was a significant improvement in quality of life in all measured domains and in quality-adjusted life years. These improvements were sustained at 2 years. All analgesia use was reduced and, in particular, opiate use fell from 28.1% prior to surgery to 16.1% at 6 months. The overall incidence of complications was 6.8% (321/4721). Gastrointestinal complications (enterotomy, anastomotic leak or fistula) occurred in 52 (1.1%) operations and of the urinary tract (ureteric/ bladder injury or leak) in 49 (1.0%) procedures (Byrne*, et al.*, 2018a).

Only one retrospective study reported outcome of patients with bowel endometriosis in whom a resection was not performed. Stepniewska *et al*. studied 155 patients: 60 underwent a segmental resection, 40 had no bowel resection, and 55 patients had deep endometriosis without bowel involvement (Stepniewska*, et al.*, 2010). Apart from significant lower recurrence rates and higher pregnancy rates in the group of patients with a segmental resection, there also was a significant regression of pain scores in that group compared to the group that had no bowel resection, because of lack of consent. Therefore, possibility of bowel resection should be discussed upfront with the patient.

Recommendations (29-31)

Clinicians can consider performing surgical removal of deep endometriosis, as it may reduce endometriosis-associated pain and improves quality of life.	⊕⊕◯◯

The GDG recommends that women with deep endometriosis are referred to a centre of expertise.	GPP

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.	GPP

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 weak recommendation and complemented with a GPP suggestion that such surgery is ideally performed in a centre of expertise, and only after the patient is informed on potential risks, benefits, and long-term effects.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question II.3).

II.3.f.1. Surgical approach for bowel endometriosis

In 2007, a systematic review reported outcome of laparoscopic colorectal resection for endometriosis as an alternative to laparotomy (Darai*, et al.*, 2007). With a conversion rate of 7.8%, this review showed feasibility and safety of a laparoscopic approach with markedly improvement of pain and gynaecological and digestive symptoms. A relatively small RCT (26 patients in each group) showed that laparoscopy was as effective as laparotomy for colorectal resection for endometriosis, in improving pain symptoms and quality of life (Darai*, et al.*, 2010b).

In another study, the same authors retrospectively studied 29 patients who underwent radical en bloc hysterectomy and colorectal resection (Darai*, et al.*, 2010a). Thirteen patients had an open approach and 16 were done laparoscopically. In both groups there was a significant improvement of dysmenorrhea, dyspareunia, asthenia, and quality of life. The laparoscopic approach had better short-term outcomes. Although this study advocated the laparoscopic approach, with comparable efficacy, it can be questioned whether hysterectomy is the treatment of choice (also see section on hysterectomy).

Discoid excision

In 4 medium-sized non-comparative prospective studies (range n=25 to n=111) outcome of discoid excision of rectal endometriosis was evaluated (Ercoli*, et al.*, 2017, Roman*, et al.*, 2015, Roman*, et al.*, 2017, Spagnolo*, et al.*, 2014). Spagnolo *et al.* studied 36 patients and reported outcome of 25 patients (11 patients were lost to follow-up) (Spagnolo*, et al.*, 2014). Median follow-up was 7 months. Discoid excision had no impact on urodynamic or anorectal function, but pain scores improved postoperatively. Ercoli *et al.* prospectively studied 33 patients and reported outcome in 30 patients, who underwent so-called laparoscopic robotic-assisted rectal nodulectomy (Ercoli*, et al.*, 2017). After mean follow-up of 27.6 months mean VAS-scores decreased significantly for dysmenorrhea, dyspareunia, dyschezia, dysuria, and chronic pelvic pain. Two prospective studies from the same group reported outcome of discoid excision with staplers (Roman*, et al.*, 2015, Roman*, et al.*, 2017). Improvement of gastrointestinal function and pain scores were observed in both studies. Although the authors concluded that discoid excision is a valuable alternative to colorectal resection in both papers, no direct comparison was made to this technique.

Segmental resection

Twelve other studies (1 RCT, 7 prospective, 4 retrospective) reported outcome of pain in patients (n=7 to n=900) after colorectal resection for deep endometriosis (Bassi*, et al.*, 2011, Garavaglia*, et al.*, 2018, Kent*, et al.*, 2016, Lyons*, et al.*, 2006, Mabrouk*, et al.*, 2012, Meuleman*, et al.*, 2011a, Ribeiro*, et al.*, 2014, Riiskjaer*, et al.*, 2018, Roman*, et al.*, 2013, Ruffo*, et al.*, 2014, Silveira da Cunha Araujo*, et al.*, 2014, Touboul*, et al.*, 2015). In all of these studies, significant improvement of all variables studied was reported. All pain-related VAS scores concerning dysmenorrhea, dyspareunia, dyschezia, dysuria, (chronic) pelvic pain, and bodily pain significantly decreased in the postoperative course. Postoperative follow-up ranged from 1 year to more than 4 years. Moreover, improvement of gastrointestinal symptoms, quality of life, sexual function, and fertility rates were also observed in these studies. In view of this, many authors conclude that laparoscopic colorectal resection improves outcome. One retrospective study further investigated the role of a radical (24 patients) *versus* a symptom-guided approach (51 patients) to treat rectal endometriosis in a before-after study design setting (Roman*, et al.*, 2013). In both study arms, there was a significant improvement in bowel function scores (KESS, GIQLI, and FIQL), and the authors concluded that a conservative approach should be chosen whenever possible. In fact, this study does not conflict with previous studies regarding radicality of treatment. Radical resection of all endometriosis nodules does not mean that a conservative attitude towards surgical technique/options could be maintained. A least traumatic, but radical resection with a more tailored /patient-centred approach with perioperative decision-making is preferred.

Comparisons between shaving, discoid excision and segmental resection

There is an ongoing debate in the literature whether shaving, discoid excision, or segmental resection with anastomosis should be used for colorectal endometriosis. Moreover, the use of electrocautery or CO_2 laser is also matter of debate and is beyond the scope of this guideline. (For surgical techniques please see (Working group of ESGE ESHRE and WES*, et al.*, 2020a, b)). In many of the studies, patient selection is questionable, because it is not always clear that both surgical options would be feasible in the presented cohort of patients.

Conservative surgery (Shaving and/or discoid excision) compared to segmental resection

In 2 studies, segmental resection *versus* more conservative-like approaches such as shaving were compared (Bourdel*, et al.*, 2018, Roman*, et al.*, 2018). Roman *et al.* performed the only published randomised controlled trial in the literature with direct comparison of 2 techniques for rectal endometriosis up to 15cm in 60 patients (Roman*, et al.*, 2018). In a multicentre study, patients were randomised to receive either segmental resection, or conservative surgery (shaving or discoid excision). The primary endpoint was the proportion of patients experiencing one of the following symptoms at 24 months follow-up: constipation, frequent bowel movements, defecation pain, anal incontinence, dysuria, or bladder atony requiring self-catherisation. At intention-to-treat analysis, there were no significant differences in functional gastrointestinal or urinary outcomes. The authors concluded that conservative surgery is feasible for large nodules of the rectum. However, this rather small study could not draw conclusions on small nodules (<20mm). Of note, temporary stoma rate was around 60% in both study arms. Bourdel *et al.* retrospectively analysed 195 patients with endometriosis of the rectovaginal septum (>2 cm in diameter). A total of 172 patients underwent rectal shaving and 23 had a segmental resection (Bourdel*, et al.*, 2018). Mean VAS scores dropped from 5.5 to 2.3 ($p<0.001$) for shaving and from 7.3 to 2 ($p<0.001$) for resection, respectively. Moreover, the authors observed significant improvement of dysmenorrhea, but no differences in quality of life. They concluded that whenever possible, shaving is the preferred technique to apply. A recent retrospective single centre series of 232 patient analysis showed that segmental resection was associated with higher complication rates compared to conservative surgery, although the difference became non-significant when corrections were made for patient characteristics (Bafort*, et al.*, 2020b).

Discoid excision compared to segmental resection

In three studies, discoid excision *versus* segmental resection (1 prospective, 1 case-control, and 1 retrospective study) was compared (Fanfani*, et al.*, 2010, Hudelist*, et al.*, 2018a, Roman*, et al.*, 2010). Hudelist *et al.* compared 32 discoid excisions with 102 segmental resections for rectosigmoidal endometriosis up to 25 cm from the anal verge (Hudelist*, et al.*, 2018a). They showed improvement of pain and fertility in both cohorts, with equal postoperative morbidity. Roman *et al.* studied 41 patients with rectal endometriosis retrospectively. Sixteen patients underwent nodule excision and 25 had a resection (Roman*, et al.*, 2010). After a mean follow-up of 26 (12-53) months they observed no significant differences in improvement of pain, but worse functional outcome after resection. Fanfani *et al.* mainly studied feasibility of discoid excision with a stapler compared to segmental resection (Fanfani*, et al.*, 2010). Although they observed improvement of endometriosis-related symptoms, no data on pain was reported.

It has been suggested that discoid resection should be the first choice in rectal endometriosis patients with unifocal endometriotic lesions less then 3 cm, while segmental resection should be chosen in high bowel lesions, and when the discoid resection is not feasible (de Almeida*, et al.*, 2014).

Shaving vs discoid excision vs segmental resection

In 3 retrospective studies, a comparison was made between 3 surgical techniques (Abo*, et al.*, 2018, Afors*, et al.*, 2016, Mabrouk*, et al.*, 2018). Abo *et al.* studied 364 patients but only reported short-term postoperative outcome without comparing pain scores or recurrence rates (Abo*, et al.*, 2018). Another

study by Mabrouk *et al.* included 392 patients with rectosigmoid endometriosis. Shaving was performed in 76%, discoid excision in 8%, and resection in 16%, respectively (Mabrouk*, et al.*, 2018). After mean follow of 43 months (12-163), there were significantly less complications in the shaving group (5.4%), *versus* discoid excision (9.1%), and resection (17.7%), respectively (p=0.004). However, no significant difference was observed in recurrence rates. The authors concluded that conservative surgery (shaving) is associated with fewer short-term complications and similar recurrence rates. Although this seems to be an attractive conclusion, the retrospective nature of the study will have inherent selection bias and compared groups were rather small. Afors *et al.* studied 92 patients with bowel endometriosis and compared shaving (n=47), discoid excision (n=15), and segmental resection (n=30) (Afors*, et al.*, 2016). Follow-up was minimum 24 months and the authors observed higher recurrence of dysmenorrhea and/or dyspareunia, and a higher re-intervention rate in the shaving group. They concluded that shaving should be avoided in big nodules, because relative risk was 2.5 for bowel resection for nodules >3 cm. A recent meta-analysis corroborates this observation in an elegant way. Risk of histologically proven recurrence for colorectal endometriosis was significantly lower after both segmental resection and discoid excision compared to rectal shaving (Bendifallah*, et al.*, 2020). The authors concluded that this important message should guide decision-making in the choice for the most appropriate surgical management.

In summary, literature is unambiguous regarding some aspects of treatment of women with colorectal endometriosis. It should be done in a multidisciplinary setting with a minimally invasive approach aiming to radically remove all endometriosis lesions. Apart from significant improvement of pain, radical treatment of deep endometriosis also positively impacts fertility outcomes (Daraï*, et al.*, 2017). For lesions on the sigmoid colon, a segmental resection should be performed. For deep endometriosis involving the rectum, a more tailored approach can be chosen. A laparoscopic approach is preferred, because it is associated with better postoperative recovery, shorter hospital stay, and better cosmetic outcome. If relevant laparoscopic experience is not available, it is recommended to refer the patient to an expert centre.

II.3.f.2. Complications of surgery for bowel endometriosis

Surgery for deep endometriosis appears possible and effective, but this is associated with significant complication rates, particularly when rectal surgery is required. The reported total intraoperative complication rate was 2.1%, and the total postoperative complication rate was 13.9% (9.5% minor, 4.6% major) (Kondo*, et al.*, 2011). There is an ongoing debate about the indication for shaving nodules as opposed to segmental resection (Donnez and Squifflet, 2010, Meuleman*, et al.*, 2011b).

The reported recurrence rates following surgery for colorectal endometriosis in the studies with longer than 2 years follow up were 5–25% (Meuleman*, et al.*, 2011b); the recurrence rates were higher in studies that reported symptomatic recurrence than in studies that reported histological recurrence (De Cicco*, et al.*, 2011).

II.3.f.3. Surgery for posterior compartment endometriosis excluding bowel endometriosis.

Endometriosis of the uterosacral ligaments and vagina

These two locations of deep endometriosis are of great clinical interest because they can be diagnosed during a clinical examination. One historic case series reports pain score at baseline and 12-month follow-up for 28 women who had complete excision of uterosacral ligament endometriosis along with excision of all of all other endometriotic lesions, including vaginal endometriosis (Chapron and Dubuisson, 1996). No complications were reported. Sixteen out of 19 women with dysmenorrhoea and 16 out of 17 women with deep dyspareunia improved. Chronic pelvic pain improved in seven out of nine cases.

Angioli *et al*. described a three-step vagino-laparoscopic approach to treatment of vaginal endometriosis (Angioli*, et al.*, 2014). The authors reported no major complications but superficial vascular injury in two cases (5.9%), ureteral stenosis two weeks after surgery in one patient (2.9%), and bowel obstruction for paralytic ileus in one patient (2.9%). A de novo endometrioma was found at 12 months after surgery and a recurrent endometrioma was evident at 24 months. For all symptoms evaluated, there was a significant improvement within 3 months after surgery ($p<0.05$) and no statistically significant difference during follow-up (at 3, 6, 12 and 24 months).

Endometriosis of the cul-de-sac

Reich *et al.* reported a series of 100 women with cul-de-sac obliteration from retro-cervical deep fibrotic endometriosis and described their operating technique (Reich*, et al.*, 1991). Forty-one of the 46 women with pain had reported improvement, (48% partial, 52% complete). Hong *et al*. reported the quality of life and pain outcomes for 390 patients with histologically proven deep endometriosis in the cul-de-sac who underwent laparoscopic excision (Douglasectomy) in a non-randomised comparative study (Hong*, et al.*, 2014). Results were stratified by whether or not concurrent hysterectomy was performed. The VAS score for pain decreased significantly after surgery in both groups (follow up time not stated), but the non-hysterectomised women (who according to the authors had a higher disease burden) had fewer significant improvements in the SF-36 subscales.

Conclusion

Due to the heterogeneity of patient populations, surgical approaches, preferences, and techniques, the GDG decided not to make any conclusions or recommendations on the techniques to be applied for treatment of pain associated with deep endometriosis.

Endometriosis of the bladder and ureters

Surgical treatment of bladder endometriosis is usually excision of the lesion and primary closure of the bladder wall. Ureteral lesions may be excised after stenting the ureter; however, in the presence of intrinsic lesions or significant obstruction, segmental excision with end-to-end anastomosis or reimplantation may be necessary.

Information on bladder endometriosis treatment was derived from small to medium size case series (Goncalves *et al.,* 2019, n=10; Chapron *et al.,* 2010, n=75; Pontis *et al.,* 2016, n=16; Kovoor *et al.,* 2010, n=21; Schonman *et al.*, 2013, n=69). Excision of endometriosis either by partial cystectomy or shaving was associated with significant improvement of pain symptoms with low complication and recurrence rates in all five case series (Chapron*, et al.*, 2010, Goncalves*, et al.*, 2019, Kovoor*, et al.*, 2010, Pontis*, et al.*, 2016, Schonman*, et al.*, 2013).

A systematic review of 17 cohort studies including 700 women analysed the laparoscopic management of ureteric endometriosis (Cavaco-Gomes*, et al.*, 2017). Typically, women with ureteric endometriosis did not complain of symptoms specific to the urinary tract. The left ureter was affected in 53.6%, bilateral disease was present in 10.6% of cases. Ureterolysis alone was performed in 579 patients, 89 underwent ureteral resection and re-anastomosis, and 32 had ureteroneocystostomy. Rectovaginal and uterosacral involvement were present in 58.8% and 47.9% of patients, respectively and concomitant ureteral and bladder endometriosis in 19.8% of patients. Conversion to laparotomy was reported in six studies in 3-6,7% of patients. Major postoperative complications occurred in 3.2% and the need for reoperation during follow-up period because of ureteral endometriosis persistence or recurrence was 3.9%. The authors felt a more conservative approach (ureterolysis) was appropriate in most patients with ureteral endometriosis.

Hudelist *et al*. 2018 reported pain and fertility outcomes in a series of 50 women with ureteric endometriosis/hydronephrosis (n=23) and bladder (n=27) endometriosis and 3 with both pathologies (Hudelist*, et al.*, 2018b). Patients were treated with either segmental bladder excision, ureterolysis/decompression, ureteric resection and end-to-end anastomosis or ureteroneocystostomy (17 women had concomitant bowel resections). After a median follow-up of 23 months, there was significant improvement in the pain symptoms and QoL.

For further surgical details of the management of bladder and ureteric endometriosis the reader is referred to the recommendations by the Working Group of ESGE, ESHRE and WES (Working group of ESGE ESHRE and WES*, et al.*, 2020a, b).

II.3.g. Nerve-sparing laparoscopy

A systematic review of four RCTs comparing conventional to nerve-sparing operative laparoscopy in painful deep endometriosis investigates the rate of urinary retention, defined as the need to self-catheterise at discharge and 90 days after surgery for painful deep endometriosis (de Resende*, et al.*, 2017). The relative risk of requiring self-catheterisation at discharge after nerve sparing surgery compared to the conventional technique was 0.19 (95%CI 0.03 to 1.17). Based on two studies, common RR for persistent urinary retention (after 90 days) was 0.16 (95%CI 0.03 to 0.84].

Since then, an additional cohort study was published on 34 women who had laparoscopic surgery for posterior compartment endometriosis (Uccella*, et al.*, 2018) reported no cases of self-catheterisation at 6-and 12-month follow-up and urinary function was not impaired by surgery. Median VAS score levels of pelvic pain were significantly decreased after surgery both at 6 (median 3, range 0-7 and 2, 0-7, respectively) and at 12 months (3, 0-8 and 2, 0-7), compared to preoperative levels (9, 1-10 and 3, 0-7, respectively) ($p < 0.0001$).

Research recommendation (R8)

The GDG recommends that nerve-sparing laparoscopy should be performed in centres of expertise and that data are collected in a standardised fashion to assess its potential benefits and risks.

II.3.h. Hysterectomy for endometriosis-associated pain

There are no RCTs on hysterectomy (with or without oophorectomy) for the treatment of endometriosis-associated pain; most published articles are retrospective case series, and there are only a few prospective studies. A non-systematic review by Martin concluded that hysterectomy for chronic non-specified pelvic pain associated with endometriosis was a successful approach in many women (Martin, 2006). It also stated that some women did not obtain any relief of pain after hysterectomy and suggested focused prospective research to determine specific response patterns. This article listed several difficulties in evaluating hysterectomy for endometriosis-associated pain, including lack of differentiation between cyclical and non-cyclical pain, difficulty in establishing whether endometriosis is the cause of pain or a co-incidental finding in a woman with chronic pelvic pain, and high variability in the rates of success among the studies.

The conclusions of this review were supported by two further publications. Shakiba *et al.* found that women who underwent hysterectomy with or without removal of the ovaries were significantly less likely to require further surgery, compared to those who underwent conservative surgery (Shakiba*, et al.*, 2008). A population-based study from Sweden also showed that hysterectomy with preservation or removal of ovaries resulted in a significant and long-lasting reduction in the pain symptoms (Sandström*, et al.*, 2020).

Other important aspects to consider are effective removal of endometriotic lesions and removal of ovaries. Many clinicians believe that surgical castration would lead to regression of remaining endometriotic lesions. Furthermore, hysterectomy with ovarian conservation was reported to have a 6-fold risk for development of recurrent pain and an 8.1-times greater risk of reoperation (Martin, 2006, Namnoum, *et al.*, 1995). This would need to be weighed against the need for hormone replacement and potential long-term impact of oophorectomy.

Recommendations (32-34)

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. Women should be informed that hysterectomy will not necessarily cure the symptoms or the disease.	⊕⊕◯◯
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.	GPP
The GDG recommends that when hysterectomy is performed, a total hysterectomy is preferred.	GPP

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 centralisation 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.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question II.3).

II.3.i Patient selection for surgery

NARRATIVE QUESTION: IS THERE A SUBGROUP OF WOMEN WITH CONFIRMED ENDOMETRIOSIS WHO RESPOND BETTER TO SURGERY THAN OTHERS?

There are few studies addressing this question. A recent systematic review identified papers that reported on the prognostic factors which were associated with a clinically meaningful reduction in endometriosis-associated pain after laparoscopic surgery (Ball, *et al.*, 2021) and included two

retrospective (Chopin, *et al.*, 2005, Ghai, *et al.*, 2020), and three prospective studies (Abbott, *et al.*, 2003, Banerjee, *et al.*, 2006, Milingos, *et al.*, 2006). Four of the five included studies indicated that stronger pain relief after endometriosis surgery was related to more severe disease prior to surgery (Banerjee, *et al.*, 2006, Chopin, *et al.*, 2005, Ghai, *et al.*, 2020, Milingos, *et al.*, 2006). There is a knowledge gap on this specific question and further research is required.

Research recommendation (R9)

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.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question II.3b).

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II.4. Medical therapies adjunct to surgery

The question on whether medical therapies are effective as an adjunct to surgical therapy considers both therapies to improve immediate surgical outcomes, and therapies aimed at secondary prevention, being prevention of recurrence of disease and/or symptoms.

A good practice point in this respect was formulated in the previous ESHRE guideline for endometriosis (Dunselman*, et al.*, 2014): "The GDG recommends that clinicians clearly distinguish adjunctive short-term (< 6 months) hormone treatment after surgery from long-term (> 6 months) hormone treatment; the latter is aimed at secondary prevention."

The evidence and recommendations are therefore separated into 'therapies to improve immediate surgical outcomes' and 'therapies for secondary prevention'. The latter is discussed in chapter IV. Endometriosis and recurrence.

PICO QUESTION: ARE MEDICAL THERAPIES EFFECTIVE AS AN ADJUNCT TO SURGICAL THERAPY?

The Cochrane review considering both pre- and postoperative treatment in relation to the management of cysts, pain, and infertility (Yap*, et al.*, 2004) was updated in 2020 (Chen*, et al.*, 2020).

II.4.a Preoperative medical treatment

With regards to preoperative treatment, the updated review shows no benefit with regards to pain, dysmenorrhea, or dyspareunia recurrence. With regards to disease recurrence, no new data were included compared to the previous version of the review. Chen *et al.* reports uncertainty regarding a difference in pelvic pain recurrence at 12 months or less (dichotomous) between presurgical medical hormonal suppression and surgery alone (RR 1.10; 95%CI 0.72 to 1.66; 1 RCT; n=262) (Chen*, et al.*, 2020). The same statement was formulated for dysmenorrhea, dyspareunia, and disease recurrence.

Recommendation (35)

It is not recommended to prescribe preoperative hormone treatment to improve the immediate outcome of surgery for pain in women with endometriosis.	⊕⊕◯◯

Justification

The guideline group confirms the recommendation from the previous ESHRE guideline (Dunselman*, et al.*, 2014). 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, vascularisation 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.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question II.4).

II.4.b Postoperative medical treatment

The review from Chen *et al.* presents the data for pain and disease recurrence in the short-term (≤12 months) and similar to the previous guideline, the data summarised for ≤12 months are considered relevant to assess the efficacy of postoperative medical treatment to improve immediate surgical outcomes (Chen*, et al.*, 2020). The interventions included were GnRH agonists, danazol, letrozole, OCP, and progestogens. Compared to surgery alone, postsurgical medical therapy may decrease pain recurrence at 12 months or less (RR 0.70; 95%CI 0.52 to 0.94; 5 RCTs; 657 patients) (Chen*, et al.*, 2020). With regards to disease recurrence, there may be a decrease in favour of postsurgical medical therapy, compared to no therapy (RR 0.30; 95%CI 0.17 to 0.54; 4 RCTs; 433 patients).

Postoperative levonorgestrel-releasing intrauterine system (LNG-IUS) was not included as an intervention in the review (Chen*, et al.*, 2020). In a randomised controlled trial, 55 patients with endometriosis and moderate-to-severe dysmenorrhea were randomised after surgery to LNG-IUS or expectant management. At 12 months follow-up, patients in the LNG-IUS group had significantly lower median values of dysmenorrhea and noncyclical pelvic pain score, a greater reduction in dysmenorrhea visual analogue scale (VAS) score (-81.0 compared with -50.0 mm) and pelvic pain VAS score (-48.5 compared with -22.0 mm). The reduction in dyspareunia VAS was comparable between the groups. Two patients in the LNG-IUS group and (7.4%) and nine in the expectant management group (39.1%) had recurrent dysmenorrhea within 1 year postoperatively (Tanmahasamut*, et al.*, 2012).

Recommendation (36)

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.	⊕⊕◯◯

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 favourable 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 (weak recommendation).

Medical therapies aimed at prevention of recurrence after surgery (secondary prevention) are discussed in chapter IV. Endometriosis recurrence.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question II.4)

References

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II.5. Medical versus surgical treatment for endometriosis

PICO Question: Are surgical therapies more effective than medical therapies for women with endometriosis with pain symptoms?

The question on whether surgical therapies are more effective than medical therapies for endometriosis-associated pain is an important clinical question. However, it has not been fully addressed in research.

Our literature search retrieved two cohort study from the same research team. In the first parallel cohort study, 154 patients were followed up for 12 months after choosing hormone treatment (progestin) or surgery for deep dyspareunia and rectovaginal endometriotic lesions. The study showed that both treatment options were effective (Vercellini*, et al.*, 2012). The cohort study included 87 women with a diagnosis of DE and indication for surgical excision of intestinal endometriosis. Of the women, 50 opted for medical treatment (OCP [n=12] or progestin [n=38]) while 37 had surgery. Six women in the medical therapy group requested surgery because of drug inefficacy (n=3) or intolerance (n=3). Seven major complications were observed in the surgery group (19%). At 12-month follow-up, 39 (78%) women in the medical therapy group were satisfied with their treatment, compared with 28 (76%) in the surgery group (adjusted OR 1.37; 95%CI 0.45 to 4.15; intention-to-treat analysis). Corresponding figures at final follow-up assessment were 72% in the former group and 65% in the latter one (adjusted OR 1.74; 95%CI 0.62 to 4.85) (Vercellini*, et al.*, 2018). Based on the high satisfaction in both groups, the authors advocated for a shared-decision approach.

For endometrioma, there are no randomised studies that compare surgery to treatment with medication, but a protocol for an RCT to answer this question was recently published. The results of the trial will provide evidence for future recommendations on whether surgical or medical therapies are more effective for endometrioma-associated pain (van Barneveld*, et al.*, 2020).

Recommendation (37)

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 between hormone treatments and surgical treatments for endometriosis-associated pain.	GPP

Justification

There is no conclusive evidence to make any definite recommendation on whether medical therapies or surgery are more effective for relieving pain in women with endometriosis. Surgery is a potential 'instant' treatment, but surgical complications are possible and often give only temporary pain relief with a considerable risk of recurrence. Medical management does not require general anaesthesia and hospitalisation, but it can be associated with short and long-term side effects and patients may need to use medical treatments for a long period.

Research recommendation (R10)

The GDG recommends sufficiently powered randomised clinical trials in different countries and cultural backgrounds to directly compare the risks, costs, and clinical outcomes of laparoscopy and empirical treatment.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question II.5)

References

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II.6. Non-medical management strategies

Non-medical management strategies are widely used by women with endometriosis. In a recent questionnaire study, it was shown that 62.5% of Swiss, Austrian, and German endometriosis patients used complementary and alternative medicine (CAM). The study also reported a link between higher usage of CAM and dissatisfaction with health care (Schwartz*, et al.*, 2019).

Amour *et al.* provided a description of 'self-management strategies' highlighting that at least 70% of people with endometriosis use heat, diet, meditation, breathing, non-prescribed drugs and alcohol (Armour*, et al.*, 2019b).

Cox *et al.* also noted a large uptake of complementary therapies and concluded that people with endometriosis have a high need for 'regaining control' and develop self-management strategies (Cox*, et al.*, 2003).

Such data show that there is a place for non-surgical and non-pharmacological alternatives for women diagnosed with endometriosis. The interventions and approaches will depend on the impact of the conditions, the patients' priorities and preferences and the availability of services.

Greco *et al.* described several different treatments such as Transcutaneous Electrical Nerve Stimulation (TENS), and psychological and physical therapies being offered to adolescents with endometriosis in Boston, though they did not evaluate the outcomes (Greco, 2003).

Self-help groups can improve quality of life, as suggested by a study in which among a group of people, 9 out of the 171 chronic pain sufferers were specifically diagnosed with endometriosis (Barlow*, et al.*, 2005).

Even with the large uptake, there are very few studies evaluating the efficacy and safety of non-medical management strategies in women with endometriosis. This is also reflected in 2 key priorities (or 'unanswered research questions') identified in the James Lind Alliance Priority Setting Partnership for Endometriosis (Horne*, et al.*, 2017).

- What is the most effective way of managing the emotional and/or psychological and/or fatigue impact of living with endometriosis (including medical, non-medical, and self-management methods)?
- What are the most effective non-surgical ways of managing endometriosis-related pain and/or symptoms (medical/non-medical)?

The previous version of this ESHRE guideline concluded that the limited research and papers did not support the use of nutritional, alternative, and complimentary therapies (Dunselman*, et al.*, 2014). This chapter elaborates on recent data for non-medical management strategies for relieving endometriosis-associated pain, and improving quality of life by including more recent studies on acupuncture, physical therapies, psychological interventions, electrotherapy and traditional Chinese medicine and nutrition. Especially on psychological therapy and exercise, studies have emerged over recent years. We did not identify evidence in women with endometriosis for other alternative or complementary therapies.

Non-medical management strategies for endometriosis-associated infertility are discussed in Chapter III.7.

PICO QUESTION: WHAT NON-MEDICAL MANAGEMENT STRATEGIES ARE EFFECTIVE FOR SYMPTOMS ASSOCIATED WITH ENDOMETRIOSIS (PAIN AND QUALITY OF LIFE)?

II.6.a. Acupuncture

Acupuncture is considered a complementary and non-invasive treatment. It is integrated in Chinese medicine whereas in Western medicine different theories and outcomes are applied and most often acupuncture is classified as CAM.

A Cochrane review in 2011 found only 1 single study that met the inclusion criteria (Xiang*, et al.*, 2002, Zhu*, et al.*, 2011). The RCT compared auricular acupuncture to Chinese herbs in 67 women with endometriosis and reported a significant reduction in pain scores for patients with severe dysmenorrhea receiving acupuncture compared to Chinese herbs. However, no difference was seen in mild-to-moderate dysmenorrhea. The review concluded that there was insufficient high-quality evidence to recommend acupuncture for patients with endometriosis. They also established that a trial would need several hundred patients to reach a clinically credible estimate of efficacy.

A meta-analysis from 2016 included 2 randomised controlled trials and 1 case report describing 2 adolescents with endometriosis (Lund and Lundeberg, 2016). One included RCT (cross-over trial) compared 'sham' acupuncture (non-specific acupuncture points) with verum acupuncture (Chinese approach) and included 101 women with endometriosis and a VAS pain score of ≥ 5 divided into 2 groups (Rubi-Klein*, et al.*, 2010). They received 10 treatments over 5 weeks and they had a break of 2 menstrual cycles before they crossed over. Patients receiving verum acupuncture reported significantly less pain and improved psychological well-being compared to the 'sham' group. However, 18 patients dropped out and there was no blinding. The other RCT included a very small sample of 18 adolescents (13–22-year-olds) comparing Japanese acupuncture (smaller needles and herbs) with sham acupuncture (not penetrating the skin) (Wayne*, et al.*, 2008). They concluded that Japanese acupuncture is a safe and effective adjunct therapy for endometriosis-related pain.

Another review by Xu *et al.* also included the study of Wayne *et al.* in addition to 9 small Chinese studies, of which 3 were not peer-reviewed publications (Xu*, et al.*, 2017). According to the authors, only one study included a placebo group and blinding but the sample was too small to draw any conclusions. The included studies compared Chinese acupuncture to Chinese medicine, sham acupuncture, and Western medicine. The reviewers were able to perform a meta-analysis for the effect on pain (based on 6 studies) and concluded that there was consistent evidence to support acupuncture to alleviate dysmenorrhea and pain (VAS), regardless of the comparison. Meta-analysis for quality-of-life outcomes was not feasible due to the variation between the studies. Overall, it was a safe treatment with little or no reported adverse effects and there are grounds to believe that acupuncture could be used as an adjunct to alleviate pain in women with endometriosis.

Although summarised in several meta-analyses, the studies on acupuncture in women with endometriosis are small, non-specific, and non-blinded. The papers included had mixed outcomes and different types of acupuncture making it difficult to evaluate them. Furthermore, questions may be raised regarding the placebo groups as any needle to skin intervention provides sensory stimulation and it is not possible to present a valid inert placebo.

Considering these aspects, only one small, non-specific, and non-blinded study of low quality could be included for supporting a recommendation on acupuncture.

It was therefore concluded that based on the current literature, no recommendation can be made about the use of acupuncture to improve quality of life and reduce pain in women with endometriosis.

II.6.b Physical therapies

II.6.b.1 Physiotherapy, massage, and trigger point release therapy

Publications focussing on women with endometriosis did not yield a lot of relevant literature to guide clinicians in terms of effectiveness and indications for physiotherapy interventions. Given the need for non-medical and alternative interventions the GDG have referred to relevant guidelines related to pelvic floor dysfunction, and a systematic review for pain relief and physiotherapy interventions for general pelvic pain. This may provide some guidance when discussing appropriate physiotherapy services with patients even though very little research was identified specifically looking at the endometriosis population.

Physiotherapy is not 'a treatment' in itself but a profession addressing human movement and function affected by injury or disease. Consequently, approaches and therapeutic options may vary. Pelvic health physiotherapists (often based in Women's health settings) may focus specifically on pelvic floor dysfunction, such as bladder, bowel, sexual and musculoskeletal issues. Physiotherapists are likely to support women with activity management such as exercises, pacing strategies and goal setting. When working with persistent pelvic pain conditions, it becomes more important to identify fears, beliefs and other psychological issues including social barriers. Physiotherapists working in pain management are likely to have developed further skills in behavioural approaches and multidisciplinary working focussing less on the end organ or tissue dysfunction, and more on responses in the nervous system and quality of life. As such, it is very difficult to extract specific components of physiotherapy treatments as the human interaction, communication skills and patient centred care will affect all interventions.

Moderate evidence exists for the effectiveness of pelvic floor exercises addressing pelvic floor dysfunction for urinary incontinence (Dumoulin*, et al.*, 2018) and this approach is also recommended by NICE for faecal incontinence (National Institute for Health and Care Excellence, 2007). NICE guidelines for pelvic floor dysfunction will shortly publish their recommendations looking at supervised pelvic muscle training to improve issues such as pelvic organ prolapse, stress and mixed urinary incontinence as well as faecal incontinence (National Institute for Health and Care Excellence, 2021). Clinicians should be aware that non-medical strategies such as pelvic floor training are available for these issues that can be associated with complications from endometriosis, but no specific research was identified for pelvic floor training for women with endometriosis.

Physiotherapists may use passive approaches such as massage and trigger point release therapy. However, a literature review of trigger point manual therapy (TPMT) for reducing chronic noncancer pain found 2 pelvic pain trials that met the inclusion criteria (Denneny*, et al.*, 2019). These studies did not demonstrate any significant reduction in pain compared to general massage (as control intervention), and overall, the review concluded that trigger point therapy cannot be recommended for chronic pain.

In a review about physiotherapy in women with pelvic pain, it was concluded that recommendations for physiotherapy should be given with caution. The review found six RCTs with significant heterogeneity and often combined with psychological and medical management making it impossible to establish the 'stand alone' value of physiotherapy input (Loving*, et al.*, 2012).

Two studies were retrieved evaluating manipulations and massage for relief of endometriosis-associated pain, but both were of too low quality to support any recommendations (Darai*, et al.*, 2015, Valiani*, et al.*, 2010).

II.6.b.2 Exercise

Exercise has a large range of benefits including improvement in mental health and decreased risk of a large number of medical conditions as described and recommended by WHO

(https://www.who.int/news-room/fact-sheets/detail/physical-activity). Supporting patients staying active and exercising are key elements of pain management programmes (British Pain Society, 2019) for people with persistent pain conditions, but the research into the specific effects on exercise on endometriosis has not been well documented.

A Cochrane review on dysmenorrhea (not specific for endometriosis) found low-quality evidence suggesting that exercise, performed at least three times per week for about 45 to 60 minutes, regardless of intensity, may provide a clinically significant reduction in menstrual pain intensity of around 25 mm on a 100 mm VAS. Given the overall health benefits of exercise, and the relatively low risk of side effects reported in the general population, women may consider using exercise, either alone or in conjunction with other treatments (Armour*, et al.*, 2019a).

Bonocher *et al.* could not make any firm recommendations from their literature review on endometriosis and physical exercises as included studies reported a mixture of outcomes. They primarily examined the risk of recurrence of endometriosis and were not able to draw any conclusion regarding pain relief or quality of life measures. The 6 studies included were poor quality, did not include any randomised controlled trials and 4 were case studies (Bonocher*, et al.*, 2014). One of the included studies, looked at various forms of physical activity in a retrospective study and concluded that there is a link between increased physical activity and less effectiveness from medication. They theorised that it may be related to the pain-relieving effect of exercise itself which meant patients found the medication did not have the same effectiveness (Koppan*, et al.*, 2010).

Awad *et al.* looked at posture, stretch and relaxation classes but demonstrated only a trend towards pain relief with no control group (Awad*, et al.*, 2017). Goncalves *et al.* used yoga as the primary intervention, in a small sample of 16 patients doing yoga and 12 patients receiving medication and one individual physiotherapy session per week (Goncalves*, et al.*, 2017). The study did show that the yoga group improved more in terms of pain relief and quality of life, but 12 patients dropped out as they could not commit to the 2 months of 4 weekly hours of yoga. The improvements may also be related to the effect of being in a group (Goncalves*, et al.*, 2016).

It was encouraging that it demonstrated that following people with endometriosis over the years demonstrate that over 80% report improvement in symptoms but the variety of activity that were reported means no recommendations or conclusions can be drawn from that study. Carpenter *et al.* similarly found that patients taking danazol reported less side-effects when they exercised, but no change in reported pain levels (Carpenter*, et al.*, 1995).

Conclusion

In summary and based on the current literature, no recommendation can be made about physical therapies or exercise and their benefit with regards to improving quality of life and reducing pain in women with endometriosis

Overall, evidence is very poor for benefit of physiotherapy in women with pelvic pain, and adverse events are unclear. Additionally, it is very difficult to extract specific components of physiotherapy interventions as the human interaction, communication skills and patient centred care will affect all interventions. As such, no recommendation was formulated on physiotherapy, massage, and trigger point release therapy.

For exercise and activity, there is also insufficient literature to make a firm conclusion of its benefit for relieving chronic pelvic pain or endometriosis-related pain. However, exercise and activity are considered part of a healthy lifestyle in general. The GDG decided a cautious recommendation, with a note on the need for further studies.

II.6.c Electrotherapy

A Cochrane review on Transcutaneous Electrical Nerve Stimulation (TENS) for chronic pain (not endometriosis specific) concluded that published literature on the subject lacks the methodological rigour or robust reporting needed to make confident assessments of the role of TENS in chronic pain management (Nnoaham and Kumbang, 2008).

One RCT looked at electrotherapy using self-applied TENS and acupuncture-like TENS for treatment of chronic pelvic pain and deep dyspareunia in women with deep endometriosis. (Mira*, et al.*, 2015). It demonstrated that both groups had significant improvements in terms of stress reduction and improvements in quality of life apart from sexual function on EHP-30.

Bi *et al.* treated 83 women with endometriosis with neuromuscular electrical stimulation and compared their outcomes after 10 weeks to 71 patients on a waiting list (Bi and Xie, 2018). No improvements were detected after 5 weeks, but after 10 weeks there was a statistically significant difference in pain on a numerical scale, Endometriosis Symptom Severity Scale and SF-36 in favour of the treatment group.

Thabet *et al.* examined the effect of pulsed high-intensity laser therapy (3 sessions per week for 8 weeks) compared to sham laser treatment, both in addition to standard hormone treatment in 2 groups of 20 women with endometriosis (Thabet and Alshehri, 2018). 85% of patients in the active treatment group reported 'complete' or 'excellent' pain relief, and there was a significant increase in quality of life on Endometriosis Health profile (EHP-5).

For all 3 studies, the conclusions should be considered with caution based on the design of the studies and the small number of patients included.

In summary, no recommendation can be made based on these studies regarding electrotherapy and the effect on quality of life or pain in women with endometriosis.

II.6.d Psychological interventions

Overall, 3 reviews were included that considered the impact of psychological interventions for symptoms associated with endometriosis (and/or in addition to surgery/other medical treatment). Trials were designed with different methodologies and based on different psychological frameworks and types of intervention. Although it is possible to investigate the validated outcomes (e.g., pain, quality of life, infertility, anxiety, and depression), it is also difficult to separate effects, as these outcomes may overlap and interact.

The reviews did not yield conclusive findings. Buggio *et al.*, in a narrative review, discussed the importance of integrating psychological interventions, including psychotherapy, in endometriosis treatment (among diet, dietary supplements, physical exercise, osteopathy, massage, acupuncture, transcutaneous electrical nerve stimulation, and Chinese herbal medicine, sexual therapy) (Buggio*, et al.*, 2017). The authors suggest that women may benefit from supportive–expressive psychotherapeutic interventions (either individual or in group) aimed at facilitating the expression of deepest thoughts and feelings about endometriosis, as well as at empowering their female identity. Van Niekerk *et al.* did a systematic review, with narrative data synthesis, on psychological interventions for endometriosis-related symptoms. They found 11 full-text studies that met the inclusion criteria, although the overall quality of studies was found to be 'weak', with a 'high' risk of bias (Van Niekerk*, et al.*, 2019). Evans *et al.* performed a systematic review on psychological and mind-body interventions for endometriosis (Evans*, et al.*, 2019). They included 12 studies, which overlap with those included by Van Niekerk *et al.*, with exception of two qualitative studies. The reviewers also note that no study has used gold-standard methodology, thus limiting the validity.

As no meta-analysis was performed, relevant individual studies included in the review are described below (Beissner*, et al.*, 2017, Hansen*, et al.*, 2017, Lorençatto*, et al.*, 2007, Meissner*, et al.*, 2010, Meissner*, et al.*, 2016).

The first study was of moderate quality and randomised patients with a history of endometriosis and chronic pelvic pain to either psychotherapy with somatosensory stimulation or waiting list control for 3 months (Meissner*, et al.*, 2016). In comparison with waiting list controls, treated patients showed improvements after 3 months in maximal and average global pain, pelvic pain, dyschezia, physical quality of life and mental quality of life. Improvements in the intervention group remained stable at 6 and 24 months, and control patients showed comparable symptom relief after delayed intervention.

Beissner *et al.* conducted a randomised controlled trial, including 67 patients with severe endometriosis-associated pain randomly allocated to a novel combination of psychotherapy and somatosensory stimulation (n=35) or waiting list control (n=32) (Beissner*, et al.*, 2017). Resting-state functional magnetic resonance imaging was used to assess brain connectivity of these patients at baseline, after 3 months of therapy, and after 6 months. The analysis focused on the hippocampus. Regression analysis showed that reduction in connectivity predicted therapy-induced improvement in patients' anxiety.

Another study included in this review supported multidisciplinary group interventions in reducing pain and depression (Lorençatto*, et al.*, 2007). This was supported by Hansen *et al.* who looked at long term outcomes after a 10-week psychological mindfulness-based programme. They found sustainable improvements on almost all scales of the endometriosis specific questionnaire EHP-30 and the generic form SF-36 in a six-year follow-up on the pilot study with 10 women (Hansen*, et al.*, 2017).

Two additional studies were retrieved from the literature. Friggi Sebe Petrelluzzi *et al.* studied 26 women with endometriosis and chronic pelvic pain. Participants took part in a therapeutic protocol involving physical and psychological therapy of 2.5-h sessions, once a week for 10 weeks. (Friggi Sebe Petrelluzzi*, et al.*, 2012). Treatment was effective in reducing perceived stress, normalizing cortisol levels, increasing vitality and improving physical functioning, but no control group was included. Farshi *et al.* conducted an RCT to determine the effects of selfcare counselling on depression, anxiety and on quality of life with 76 women with endometriosis. Participants were randomly assigned to either intervention group (seven weekly self-care group counselling sessions) or control group. Participants were interviewed by the researcher before and after 4 weeks using BDI, STAI and SF-36 Quality of Life Questionnaire. Women in the counselling group showed significant lower anxiety values and a significantly higher quality of life after the intervention, compared to the control group. However, participants were included up to 5 years after their (laparoscopic) diagnosis, the majority indicated their post-endometriosis-treatment condition as “recovered” and no current symptoms were collected; thus limiting the significance of the found efficacy.

In summary, no recommendations can be made regarding the effectiveness of psychological approaches to improve pain and quality of life in women with endometriosis. However, it is vital that clinicians are aware of the psychological impact of living with pain, infertility and functional pelvic issues and consider what access there is to psychological support.

Overall, 2 reviews and 2 additional studies were included that considered the impact of psychological interventions for symptoms associated with endometriosis (and/or in addition to surgery/other medical treatment). The findings in both reviews regarding the effectiveness of psychological and mind-body interventions for endometriosis-related symptoms remain inconclusive. Mostly, the studies were of low quality. Trials were designed with different methodologies and based on different psychological frameworks and types of intervention. Although it is possible to investigate the various outcomes (e.g.,

pain, quality of life, infertility, anxiety, and depression) separately, it is also difficult to separate effects, as these outcomes may overlap and interact.

II.6.e Nutrition

There has been much postulation that diet may affect endometriosis symptoms, which may be based on observation that diet can affect several processes such as inflammation, prostaglandin metabolism and estrogen activity. Still, there are very limited studies, of limited quality, evaluating the benefit of dietary interventions and their effect on endometriosis symptoms.

A review by Hansen *et al,* included six studies reporting that omega-3 fatty acids have a positive effect on dysmenorrhoea with reduced pain intensity, duration, and lower use of painkillers (Hansen and Knudsen, 2013). In the review of Huijs and Nap, 4 studies were included, all showing significantly decreased pain scores after use of fatty acids, which were not found in controls (Huijs and Nap, 2020). With regards to vitamin D, the review included 2 studies with opposite results. A small more recent RCT comparing the effect of a vitamin D supplement, fish oil (Omega-3 fatty acids supplement) and placebo, on pain scores, reported a significant improvement in pain scores after vitamin D supplementation, but reported a similar effect in the placebo group (Nodler*, et al.*, 2020). A more modest improvement was observed in patients receiving fish oil.

The review of Huijs and Nap. further reported that antioxidants, gluten, and soy were not well studied. They concluded that nutrients with direct or indirect anti-inflammatory properties might have an effect on endometriosis-related pain, but evidence is not yet available for development of a specific endometriosis diet (Huijs and Nap, 2020).

When looking at the literature for diet it must be kept in mind that women with endometriosis may change their diets to ameliorate the symptoms. With regards to dietary intake, the study of Savaris *et al.* found a significantly lower intake of poly-unsaturated fatty acids and a significantly higher intake of fibre in women with endometriosis (Savaris and do Amaral, 2011). In the same study, the authors did not find any difference in antioxidants in the diet of women with or without endometriosis, whereas Mier-Cabrera *et al.* in a reasonable sized study (n=163) found lower dietary intake of antioxidant vitamins A, C and E in women with endometriosis (Mier-Cabrera*, et al.*, 2009).

The study of Schink *et al*. provides a detailed and differentiated analysis of the nutrient intake in women with endometriosis and controls, as well as information on food intolerances, allergies, and gastrointestinal symptoms. The study showed a higher prevalence of food intolerances (25.6% vs 7,7%), allergies (57% vs 31%) and gastrointestinal symptoms (77% vs 29%) in women with endometriosis compared to controls. The nutrient intake also differed significantly with lower intake of animal proteins, vitamin C, vitamin B12 and magnesium. The authors suggested that a dietary intervention by a professional nutritionist may help to reduce disease burden in women with endometriosis (Schink*, et al.*, 2019).

Finally, the data of a qualitative study provides insight in the motivation of women with endometriosis to make and maintain dietary changes (Vennberg Karlsson*, et al.*, 2020). The participants (n=12) made individual dietary changes, mainly consisting of excluding or decreasing their intake of gluten, dairy products and increasing their intake of carbohydrates, and increasing fruit, vegetables, and fish. From a thematic analysis, the authors concluded that the participants experienced decreased symptoms of endometriosis (pain and fatigue) and gained a greater understanding of their bodies after making individual dietary changes.

II.6.f Traditional Chinese Medicine

The evidence for Chinese Medicine (CM) from the reviewed literature was not robust and studies were generally poorly constructed. There is the associated problem with Western society clinicians applying CM therapy in a Western medical setting. Only two studies were reviewed as they were better quality, but both had a high dropout rate, thus rendered the study by Flower *et al.* too small to apply any statistical analysis (Flower*, et al.*, 2011). The second study did not find any significant difference between the pain scores in the two groups CM and diet however there was no blinding and no placebo (Zhao*, et al.*, 2013)

In summary, based on the current literature, no recommendation can be made about the use of nutrition or Traditional Chinese Medicine to improve quality of life and reduce pain in women with endometriosis. Based on a few studies clinicians may suggest fish oils as an alternative to more harmful anti-inflammatories.

The literature and research into Chinese Medicine are primarily concerned with interventions and outcomes that are not commonly used in Western medicine. The studies are very heterogeneous and no recommendations can be made. With regards to nutrition, data are summarised in well constructed systematic review, but the included data are derived from small studies without proper controls, limiting meta-analysis and any firm conclusions.

Overall recommendation (38)

The GDG recommends that clinicians discuss non-medical strategies to address quality of life and psychological well-being in women managing symptoms of endometriosis. However, 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.	GPP

Justification

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 women are searching for alternative ways of managing and coping without or alongside surgical and pharmacological interventions.

Women diagnosed with a condition with an unclear aetiology and prognosis can experience life changing consequences reporting pelvic pain, painful periods and subfertility often needing long term support to manage and cope (NICE, 2017). Given the lack of literature mentioned above, it would seem reasonable to draw on some of the recommendations in chronic pelvic pain. EAU guidelines (2018) strongly recommend the provision of a multidisciplinary approach to pain management in the gynaecological aspect of the management of chronic pelvic pain. It is important that women with endometriosis have options addressing psychological, sexual, and physical factors to improve quality of life even when pain cannot be reduced. No specific pain management programmes for endometriosis have been identified, and the very limited literature supporting specific programmes for pelvic pain do not include any trials but show a trend of improvements in both pain and quality of life measures in small samples pre- and post intervention.

This highlights the importance of giving the woman the opportunity to gain information about non-medical strategies in specialist pain management services with the expertise in managing complex abdomino-pelvic pain, and the potential benefits of local support groups which is also recommended by NICE (2017).

Research recommendation (R11)

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.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question II.6)

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III. Treatment of endometriosis-associated infertility

Women with endometriosis are confronted with one or both of two major problems: endometriosis associated pain, infertility, or both (Tomassetti and D'Hooghe, 2018). For clarity, the GDG decided to separately discuss the evidence on pain as the outcome in chapter II; infertility as an outcome is addressed in this chapter.

For the literature searches, the outcomes included were live birth rate, pregnancy rate, multiple pregnancy rate, miscarriage rate, ectopic pregnancy, teratogenicity, and side effects of treatment. It should be noted that although live birth rate is the most relevant outcome, most studies only report on (biochemical or clinical) pregnancy rates. An increase in pregnancy rate could be an indication of live birth rate but does not necessarily translate to an increase in this outcome.

The first part of this chapter deals with treatments (medical, surgical, non-pharmacological) for endometriosis-associated infertility, that is, treatments that improve the spontaneous pregnancy rate. Medically assisted reproduction and adjunctive treatments are discussed in the second part of the chapter (section III.4). In the last part of the chapter, the impact of endometriosis on pregnancy and obstetric outcome is discussed, as well as indications for ART after surgery, and indications for fertility preservation.

III.1. Medical treatment

PICO Question: Are hormone/medical therapies effective for treatment of endometriosis-associated infertility?

III.1.a. Ovarian suppression

The question as to whether hormone therapy has any role in the treatment of endometriosis associated infertility has been thoroughly evaluated in a systematic Cochrane review (Hughes*, et al.*, 2007). The review does not evaluate individual hormone treatments used in the treatment of pain associated with endometriosis but considers as a group all therapies that result in ovarian suppression. Thus, strictly speaking, the assessment is confined to the role of ovarian suppression as a therapeutic modality to improve fertility.

In the analysis evaluating the effect on (clinical) pregnancy rate after the use of any ovulation suppression agent versus placebo or no treatment 12 trials were included (Hughes*, et al.*, 2007). The review reported 88 pregnancies in 420 women who received an ovarian suppression agent compared with 84 pregnancies in 413 women receiving no treatment or placebo, and thus concluded that there is no evidence of benefit on pregnancy outcomes, although data on live birth are not available. The OR for pregnancy across trials was 0.97 (95%CI 0.68 to 1.37) for all women randomised, and 1.02 (95%CI 0.69 to 1.50) for women clearly identified as subfertile (80 pregnancies in 287 women receiving treatment vs 73 in 270 controls, i.e. women receiving placebo or no treatment). Furthermore, also other comparisons (all ovarian suppression agents versus placebo or no treatment, all drugs with the exception of danazol versus placebo or no treatment, danazol versus other ovarian suppression, GnRH agonists versus oral contraceptives) failed to show any differences in pregnancy rate, even though the authors stated that there is a reasonable body of evidence with little inconsistency and minimal

evidence of heterogeneity. The published evidence does not report on more severe disease, as well as on live birth since surrogate markers were evaluated only. Similarly, there is a significant lack of reported data on adverse pregnancy outcomes, such as miscarriage and ectopic pregnancy. Most included articles were published before 2000, but also at a revision in April 2009 no new relevant data were identified, and the review was therefore closed and will no longer be updated.

Thus, it is clear that as sole treatment for endometriosis-associated infertility, recognised therapies that suppress ovulation in general are ineffective and should not be used.

Recommendation (39)

In infertile women with endometriosis, clinicians should not prescribe ovarian suppression treatment to improve fertility.	⊕⊕◯◯

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 randomisation for ovarian suppression or no treatment. This observation complicates any recommendations regarding ovarian suppression and post-surgical ovarian suppression, discussed in the following section.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question III.1)

III.1.b. Hormone or medical therapies as an adjunct to surgical therapy

Although ovarian suppression in general does not appear to have an advantage on subsequent fertility as pointed out above (see III.1.a), and surgery does increase natural fertility (see III.2), it is still of interest to evaluate whether in the perioperative period ovarian suppression may have an added benefit. The effectiveness of medical therapies for hormone suppression before, after, or both before and after therapeutic surgery for endometriosis for increasing pregnancy rates (next to for improving painful symptoms and reducing disease recurrence) has been assessed in a Cochrane review by Chen and colleagues (Chen*, et al.*, 2020), which included a total of 25 trials in 3378 women with endometriosis. This review replaces the one by Furness *et al.* cited in the previous version of this guideline, and it considered RCTs on any form of systemic medical therapy for hormone suppression (GnRH agonist, danazol, OCP, progestogens, gestrinone or combinations) at any dosage for a period of at least three months before or after surgery (Yap*, et al.*, 2004).

The effect of pre-surgical (hormone suppression) medical therapy for the improvement of pregnancy rates - as compared to surgery alone - was found to be uncertain (RR 1.18, 95%CI 0.97 to 1.45), as it was based on only one RCT (n=262) of very low quality (Chen*, et al.*, 2020).

The difference in pregnancy rate between postsurgical and presurgical medical hormone suppression therapy in the review by Chen *et al.* was found to be uncertain (RR 1.08, 95%CI 0.90 to 1.30: 1 RCT, 273 patients). The evidence suggests that if the pregnancy rate is assumed to be 60% among women with postsurgical medical hormone suppression alone, the chance following presurgical medical hormone suppression would be between 54% and 78%. No trials were identified to compare pre- and postsurgical medical therapy with surgery alone or post-surgical medical therapy (Chen*, et al.*, 2020).

The review by Chen *et al.* concludes that surgery plus postsurgical medical therapy probably increases pregnancy rate compared to surgery plus placebo or no medical therapy (RR 1.19, 95%CI 1.02 to 1.38; 11 RCTs, 955 patients; I2=27%). This suggests that if the chance of pregnancy following surgery is 34%, the chance following surgery and postsurgical medical therapy would be between 35% and 48% (Chen, *et al.*, 2020). The review included a mix of studies assessing pregnancy rates both after natural conception and MAR, and does not report on time to pregnancy, nor on the duration of hormone treatment.

Recommendations (40-41)

Women seeking pregnancy should not be prescribed postoperative hormone suppression with the sole purpose to enhance future pregnancy rates.	⊕⊕◯◯

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.	⊕⊕◯◯

Justification

Although the review by Chen concludes that there is moderate quality evidence supporting postsurgical medical therapy for improving pregnancy rates, this evidence should be interpreted with caution. Firstly, the review provides indirect evidence for the current question, as the meta-analysis includes studies reporting on pregnancy rates after both spontaneous conception and MAR, while the PICO focusses specifically on natural conception rates. The evidence was downgraded for indirectness. Secondly, rather than pregnancy rates, the total time to pregnancy should be considered as the primary outcome. Chen *et al.* acknowledges that women with subfertility due to endometriosis may not accept treatment that may reduce or delay their chance of conceiving after a surgical treatment. It is clear that a delayed start of attempted conception due to hormone suppression should be considered in decision-making. Thirdly, the GDG challenges the conclusion of the review and considers the reported RR of 1.19 (1.02 to 1.38), should be interpreted as evidence of no harm of ovarian suppression after surgery rather than benefit. Finally, the GDG questions the quality of some of the included studies in the review.

Based on these considerations, 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 (weak 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."

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question III.1)

III.1.c. Other medical treatments

As endometriosis is associated with inflammation, anti-inflammatory drugs are potentially of interest to be evaluated as an alternative approach. The effects of pentoxifylline, which has anti-inflammatory properties, in subfertile premenopausal women were evaluated in a recent updated Cochrane systematic review (Grammatis, *et al.*, 2021). In this review, based on three RCTS in 285 patients, the

evidence of the effect of pentoxifylline versus placebo on clinical pregnancy rates is very uncertain (OR 1.38; 95%CI 0.91 to 2.10), no trials reported the effects of pentoxifylline on the odds of live birth rate or adverse events. Data on the improvement of endometriosis-related symptoms i.e. overall pain, were equally very uncertain.

Since endometriosis is an estrogen-dependent disease, Alborzi *et al.* performed a RCT to assess the effect of the anti-estrogen (aromatase inhibitor) letrozole on natural pregnancy rates after surgical treatment of endometriosis (Alborzi*, et al.*, 2011). This study included 144 infertile women, randomised into 3 groups: group 1 (47 cases) received letrozole for 2 months, group 2 (40 patients) received triptorelin for 2 months and group 3 (57 patients, control group) did not receive any medication. All patients were followed up for at least for 12 months after restoration of a regular cycle. Pregnancy rates were similar in all groups (23.4%, 27.5% and 28.1%, resp.), the authors concluded that there was no benefit of the administration of letrozole to improve pregnancy rates. Of note, it is not stated whether some patients received medically assisted reproduction treatment during the follow-up period. Also, the use of letrozole for the purpose of ovulation induction was not examined.

Recommendation (42)

In infertile women with endometriosis, clinicians should not prescribe pentoxifylline, other anti-inflammatory drugs or letrozole outside ovulation-induction to improve natural pregnancy rates.	⊕◯◯◯

Justification

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).

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question III.1)

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III.2. Surgical treatment

The current section focusses on the efficacy and safety of surgery for increasing the chance of pregnancy in women with endometriosis. Technical guidance on surgical techniques for surgery in endometriosis has been previously published by a working group of ESGE, ESHRE and WES (Working group of ESGE ESHRE and WES, *et al.*, 2020a, b, Working group of ESGE ESHRE and WES, *et al.*, 2017a, Working group of ESGE ESHRE and WES, *et al.*, 2017b).

PICO Question: In women with endometriosis, is surgery effective to increase the chance of natural pregnancy?

The question on whether surgery is effective to increase the chance of natural pregnancy was covered in a recent Cochrane review (Bafort, *et al.*, 2020). Based on moderate quality evidence from 3 RCTs mainly on peritoneal endometriosis (see also III.2.a), the review concluded that laparoscopic surgery increases viable intrauterine pregnancy rates confirmed by ultrasound compared to diagnostic laparoscopy only (OR 1.89; 95%CI 1.25 to 2.86).

A similar conclusion was formulated from a recent network meta-analysis showing that pregnancy rate was significantly increased following surgical laparoscopy compared with placebo (OR 1.63; 95%CI 1.13 to 2.35) (Hodgson, *et al.*, 2020).

Jin *et al.* reported that live birth rate was significantly increased after laparoscopic surgery (relative risk [RR] 1.52; 95%CI 1.26 to 1.84, 4 studies; 741 patients) (Jin and Ruiz Beguerie, 2014).

III.2.a Peritoneal endometriosis

Although the Cochrane review does not specifically address endometriosis subtypes, it could only identify and include trials on rASRM stage I/II endometriosis (Bafort, *et al.*, 2020). Therefore, their findings could be extrapolated to peritoneal endometriosis (or at least the absence of large endometrioma and/or deep lesions with extensive adhesions). Although laparoscopic surgery was found to increase (natural) viable intrauterine pregnancy rates, no data were found on live birth rates. It should also be noted that none of the studies discussed were stratified according to the Endometriosis fertility Index (EFI).

III.2.b. Ovarian endometriosis

We did not find any RCTs comparing fertility outcomes after surgery for endometrioma in comparison with expectant management, nor studies exploring the indication for surgery depending on the size of the cyst.

A review by Alborzi *et al.* reported that, based on the combined results of 8 studies, the pregnancy rate after surgery for endometrioma was 43.8% (95%CI 22.5 to 66.4) and showed this was not significantly different from other treatments, such as surgery combined with ART, ART only or aspiration ± sclerotherapy + ART (Alborzi, *et al.*, 2019).

Surgical treatment of endometriomas is mainly performed by 2 types of procedures: cystectomy (excision of the cyst wall) and ablation (destruction of the inner surface of the cyst wall in situ). Regarding surgical technique, a review from 2013 reported that pregnancy rates were higher in patients

that underwent cystectomy when compared to fenestration/coagulation (RR 2.64; 95%CI 1.49 to 4.69) and compared to CO_2 laser vaporisation (RR 0.92; 95%CI 0.30 to 2.80) (Dan and Limin, 2013).

A recent comparative study reported pregnancy rates that were similar after laparoscopic stripping technique (72.2%) or cyst vaporisation with CO_2 fibre laser (74.3%). However, spontaneous pregnancy rate was higher after laparoscopic stripping (55.5% vs 35.9%) (Candiani, *et al.*, 2020).

It should be noted that none of the studies discussed were stratified according to the Endometriosis Fertility Index (EFI).

III.2.c. Deep endometriosis

In a systematic review by Meuleman *et al.*, it was shown that only a minority of surgical studies on deep endometriosis (with bowel involvement) report on postoperative pregnancy rates (37%, 18/49 studies) (Meuleman, *et al.*, 2011). Unfortunately, in most studies, the number of patients wishing to conceive prior to or after surgery is not clear, the distinction between active child wish, passive child wish, completed child wish and absent child wish is not made and likewise the mean period for conception following surgery and the spontaneous/assisted reproduction nature and outcome of the pregnancies are often not reported (Meuleman, *et al.*, 2011). The review of Cohen *et al.* reported the preoperative and postoperative spontaneous pregnancy rates in women with DE with and without bowel involvement. In women without bowel involvement, there were no data on preoperative pregnancy rates, but postoperative pregnancy rates were 50.5% (95%CI 46.8 to 54.1). In women with DE and bowel involvement, the postoperative spontaneous pregnancy rate was 28.6% (95%CI 25 to 32.3) (Cohen, *et al.*, 2014). Similar data were reported by Iversen *et al*, who also reported a difference based on the study types, spontaneous pregnancy rate was 49% (n=136) and 21% (n=184) in 4 retrospective and 3 prospective studies respectively (Iversen, *et al.*, 2017).

Vercellini *et al.* focused on spontaneous pregnancy rates after surgery for rectovaginal and rectosigmoid endometriosis in women that were infertile before surgery. Based on 11 studies, a mean postoperative conception rate (infertile and spontaneous PR) of 24% (95%CI 20 to 28%; 123/510) was reported, while the mean postoperative conception rate was 39% (95%CI 35 to 43%; 223/571) when preoperative fertility status and IVF performance were not considered (OR 0.50, 95%CI 0.38 to 0.65%) (Vercellini, *et al.*, 2012).

Again, it should be noted that none of the studies discussed were stratified according to the EFI.

Recommendations (43-46)

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.	⊕⊕◯◯
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.	⊕◯◯◯
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.	⊕◯◯◯

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.	GPP

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 weak 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 (Bafort*, et al.*, 2020).

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.

The role of diagnostic laparoscopy in the context of the fertility work-up will be covered in the ESHRE Guideline on Unexplained infertility (in development).

Research recommendation (R12)

In patients without a clear indication for ART, the value of surgery for ovarian and deep endometriosis and its effect on natural pregnancy rates should be evaluated. Such studies should consider patient age, endometrioma bilaterality and size, previous surgeries, adenomyosis and other factors affecting fertility.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question III.2)

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III.3 Assessing the need for assisted reproduction after surgery

NARRATIVE QUESTION: WHICH PATIENTS NEED TREATMENT WITH ASSISTED REPRODUCTION TECHNOLOGY AFTER SURGERY?

Before and after surgery for endometriosis, those individuals who wish to become pregnant should be counselled objectively on their subsequent chances of achieving a pregnancy. To this purpose, the Endometriosis Fertility Index (EFI) was developed (Adamson and Pasta, 2010) as an end-of-surgery scoring system that predicts non-ART pregnancy rates (natural conception or IUI) after surgery. It was derived from prospective analysis of clinical data and has since been (externally) validated in over 30 studies, of which the majority were evaluated in a meta-analysis (Vesali*, et al.*, 2020) confirming its good performance despite substantial heterogeneity between studies. By scoring patient-related factors (age, duration of subfertility and history of prior pregnancy) and surgical factors ('least function score' of the tubes and ovaries, endometriosis lesion and total score as extracted from the rASRM staging) factors, a score between 0 and 10 is generated. This score is strongly correlated with postoperative non-ART pregnancy rates and can therefore be used to counsel patients on their reproductive options, although it assumes normal gamete function. Its high reproducibility (Tomassetti*, et al.*, 2020) further supports its use as an important clinical decision tool. When used as a system to decide on postoperative ART, healthcare costs have also been shown to be reduced through optimal patient selection (Ferrier*, et al.*, 2020).

Additionally, as it has been shown that the end-of-surgery EFI can be estimated accurately prior to surgery, this estimation could be used as an instrument to guide joint physician–patient decision-making between surgery, ART, or other fertility management options for the individualised treatment of women with endometriosis-related infertility (Tomassetti*, et al.*, 2021), although this is the only study to date on this subject.

Conclusion

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.

Research recommendation (R13)

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.

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III.4. Medically assisted reproduction

PICO Question: Is Medically Assisted Reproduction effective for infertility associated with endometriosis?

III.4.a. Intrauterine insemination in women with endometriosis

There are very few studies assessing the efficacy of intrauterine insemination (IUI), with or without ovarian stimulation (OS), in women with endometriosis. In one RCT live birth rates were compared in women with minimal to mild endometriosis; 53 patients underwent ovarian stimulation with gonadotrophins and IUI treatment and 50 expectant management. The live birth rate was 5.6-times higher in the treated couples than in the control group (95%CI 1.18 to 17.4) (Tummon*, et al.*, 1997). In an initially randomised and subsequently longitudinal study, Nulsen and co-workers compared gonadotrophins + IUI with urine LH-timed IUI alone. In 57 couples with minimal or mild endometriosis the biochemical pregnancy rate (PR) was 5.1-times higher than with IUI alone (95%CI 1.1 to 22.5) (Nulsen*, et al.*, 1993).

Indirect evidence can be derived from studies comparing the outcomes of IUI in women with endometriosis to couples with (unexplained) infertility.

In a cohort study, Omland and colleagues compared one cycle of clomiphene citrate + HMG/FSH against HMG/FSH with artificial insemination with partner's sperm (IUI with or without intraperitoneal insemination (IPI)) in couples with unexplained infertility (119 couples) or with stage I/II endometriosis (49 couples, diagnostic laparoscopy only). PRs were significantly higher in the women with unexplained infertility (33.6% vs 16.3%) (Omland*, et al.*, 1998). In a case control study, PRs following OS + homologous insemination were as high in women with stage I/II endometriosis within 6 months of surgical treatment as in women with unexplained infertility (PR/cycle 20% vs 20.5%) (Werbrouck*, et al.*, 2006).

In a retrospectively analysis of 65 patients with surgically confirmed ASRM stages III/IV endometriosis with at least one patent tube, IUI with OS up to a maximum of six cycles compared to three times IUI without OS followed by up to three times IUI with OS significantly increased cumulative ongoing pregnancy rate (40.0% vs 15.6%) (van der Houwen*, et al.*, 2014).

Kim and co-workers, in an RCT, compared the use of long OS protocol (LP) and ultralong OS protocol (ULP) of GnRH agonist prior to IUI in 80 women (all stages of endometriosis). No difference in the clinical PR was found between protocols in women with minimal or mild endometriosis. In women with stage III/IV endometriosis, the clinical PR per cycle was significantly higher in the ULP group (50.0% (10/20)) compared with the LP group (19.0% (4/21)) (Kim*, et al.*, 1996).

Recommendations (47-48)

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.	⊕◯◯◯

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.	⊕◯◯◯

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 (weak 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 (Werbrouck, *et al.*, 2006).

All studies in endometriosis mostly used gonadotrophin for OS. Anti-estrogen therapy (clomiphene citrate and letrozole) could be an option, based on indirect evidence from studies of unexplained infertility (Danhof, *et al.*, 2018, Diamond, *et al.*, 2015), but anti-estrogen therapy for OS prior to IUI has not been studied in women with endometriosis.

Although one small sized RCT suggests higher clinical pregnancy rate with prolonged GnRH agonist suppression prior to IUI (Kim, *et al.*, 1996), this approach cannot be recommended due to the relatively low success rate of IUI after such a prolonged treatment and the associated side effects.

In patients with moderate to severe endometriosis, the benefit of ovarian stimulation with IUI is unclear as only retrospective low evidence data are available (weak recommendation).

Research recommendation (R14)

Studies should clarify whether IUI with or without ovarian stimulation is a relevant option for women with (different subtypes of) endometriosis. In addition, the value of EFI to predict the relevance of IUI could be further investigated.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question III.4)

III.4.b. Assisted reproductive technology in women with endometriosis.

To our knowledge, there are currently no randomised trials evaluating the efficacy of ART versus no intervention in women with endometriosis. Indirect evidence can be derived from studies comparing the outcomes of ART in women with endometriosis to women without endometriosis.

In a systematic review and meta-analysis from 2013, Harb and colleagues included 27 observational studies and a total of 8984 women and reported significantly lower fertilisation rates (relative risk [RR] 0.93; 95%CI 0.87 to 0.99; 7 studies; 2044 patients), with no significant reduction in implantation, clinical pregnancy, or live birth rates in women with ASRM stage I/II endometriosis compared to women without endometriosis (Harb, *et al.*, 2013). In women with stage III/IV endometriosis, a reduced implantation rate (RR 0.79; 95%CI 0.67 to 0.93; 8 studies; 923 patients) and clinical pregnancy rate (RR 0.79; 95%CI 0.69 to 0.91; 14 studies; 521 patients) was observed, and a trend towards reduced live birth rates (RR 0.86; 95%CI 0.68 to 1.08; 9 studies; 312 patients).

Another systematic review and meta-analysis made similar conclusions based on similar studies (Hamdan, *et al.*, 2015). They investigated the influence of endometriosis on ART outcomes reported no difference in live birth rates per woman when comparing women with versus without endometriosis (odds ratio [OR] 0.94; 95%CI 0.84 to 1.06; 13 studies; 12,682 patients). The clinical pregnancy rates (OR 0.78; 95%CI 0.65 tot 0.94; 24 studies; 20757 patients) and the mean number of oocytes retrieved per cycle (mean difference [MD] -1.98; 95%CI -2.87 to -1.09; 17 studies; 17593 cycles) were lower in patients with endometriosis. Subgroup analysis revealed that all of the outcomes were comparable in women with stage I/II endometriosis and no endometriosis; live birth rate (OR 0.96; 95%CI 0.82 to 1.12; 8 studies; 4,157 patients), clinical pregnancy rate (OR 0.84; 95%CI 0.69 to 1.03; 15 studies; 9,692

patients), and mean number of oocytes retrieved per cycle (MD –0.58; 95%CI, 21.16 to 0.01; 11 studies). In contrast, in women with stage III/IV endometriosis a significantly lower mean number of oocytes retrieved (MD 21.76; 95%CI 22.73 to 0.79; 14 cycles; 9172 patients), pregnancy rate (OR 0.60; 95%CI 0.44 to 0.81; 15 studies; 9,471 patients) and live birth rate (OR 0.77; 95%CI 0.64 to 0.92; 8 studies) were reported.

A total of 347,185 autologous fresh and frozen cycles from The Society for Assisted Reproductive Technologies (SART) database were analysed to assess the impact of endometriosis (alone or in combination with other infertility diagnoses) on ART outcomes (Senapati*, et al.*, 2016). The diagnosis of endometriosis was associated with a significant decrease in live birth rate (risk ratio [RR] 0.94; 95%CI 0.91 to 0.97), lower oocyte yield (RR 0.91; 95%CI 0.91 to 0.92), and lower implantation rates (RR 0.94; 95%CI 0.93 to 0.96) after ART. However, the association of endometriosis and ART outcomes was confounded by other infertility diagnoses. Endometriosis, when associated with other alterations in the reproductive tract, had the lowest chance of live birth. In contrast, for the minority of women who have endometriosis in isolation, the live birth rate is similar or slightly higher compared with other infertility diagnoses.

In a more recent retrospective single centre cohort study comparing 531 patients with endometriosis to 737 with unexplained infertility after a first embryo transfer, a 24% reduction in the likelihood of a live birth was demonstrated in women with endometriosis (OR 0.76; 95%CI 0.59 to 0.98) with an increasing effect associated with the severity of the disease (Muteshi*, et al.*, 2018). Furthermore, women with endometriosis had fewer oocytes retrieved, lower blastocyst transfer and a significantly reduced implantation rate.

Murta and colleagues conducted a retrospective study from 1995 to 2011 of patients undergoing 27294 ART cycles using data of the Latin American Registry maintained by the Latin America Network of Assisted Reproduction (REDLARA) (Murta*, et al.*, 2018). A total of 7496 patients with endometriosis only, tubal factor, and unexplained infertility were included in the study. Patients were divided into two groups: endometriosis group, comprising 1749 patients who underwent ART due to endometriosis only and control group, with 5747 patients subjected to ART due to tubal factor or unexplained infertility. They concluded that endometriosis does not affect the outcome of patients subjected to ART and although patients with endometriosis present lower number of oocytes and higher cancelation rate, these shortcomings do not reduce pregnancy and live birth rates.

The impact of endometrioma on ART reproductive outcomes was summarised in a recent review (Alshehre*, et al.*, 2020). The number of oocytes (weighted means difference; WMD -2.25; 95%CI 3.43 to - 1.06) and the number of MII oocytes retrieved (WMD -4.64; 95%CI 5.65 to -3.63) were significantly lower in women with endometrioma versus controls (women without endometrioma and/or tubal or male-factor infertility). All other outcomes, including gonadotrophin dose and duration, the total number of embryos and high-quality embryos, clinical pregnancy rate, implantation rate and live birth rate were similar in women with endometrioma and controls.

III.4.b.1 Type of OS protocol

Several trials and studies evaluated GnRH agonist versus GnRH antagonist ovarian stimulation protocols in women with endometriosis. An RCT including 246 women with stage I/II endometriosis and endometrioma showed that the implantation rate and clinical PR after OS in a GnRH antagonist cycle were not inferior to those for a GnRH agonist protocol (Pabuccu*, et al.*, 2007). An observational retrospective analysis of 1180 cycles with the propensity score matching failed to demonstrate a difference in clinical PR between GnRH agonist and GnRH antagonist protocols in patients with stage I-IV endometriosis (Rodriguez-Purata*, et al.*, 2013).

In studies comparing the long GnRH agonist and GnRH antagonist protocols, no difference in ongoing PR was observed between the 2 OS protocols in patients who previously underwent laparoscopic endometrioma resection surgery (Bastu*, et al.*, 2014). Kolanska *et al.* performed a retrospective analysis of 284 IVF cycles, and reported that women with endometriosis experienced higher pregnancy and live birth rates after fresh embryo transfer but not after frozen cycle when long GnRH agonist protocols were compared to GnRH antagonist protocols (Kolanska*, et al.*, 2017). The cumulative live birth rates per cycle were not different between the two groups. Comparison of long GnRH agonist and GnRH antagonist ART protocols was further conducted in an observational retrospective cohort study including 386 women subdivided into two groups (endometriosis stage I/II and endometriosis stage III/IV) (Drakopoulos*, et al.*, 2018). A tendency toward higher biochemical and clinical pregnancy and live birth rates (42.8% vs. 26.7%) was noted in favour of GnRH agonist in patients with stage I/II endometriosis whereas no difference was observed in the endometriosis stage III/IV group.

III.4.b.2 MAR and risks

In a systematic review, low quality evidence suggested that ovarian stimulation with IUI might increase the risk of recurrence whereas moderate quality evidence suggested that ovarian stimulation for ART did not increase the risk of recurrence or worsen pain symptoms (Somigliana*, et al.*, 2019). Moreover, the effect on endometriomas seems minimal. ART and endometriosis recurrence are discussed in section IV.1.c.

In a series of 214 women with endometriomas undergoing oocyte retrieval for IVF/ICSI under antibiotic prophylaxis, no pelvic abscess was recorded (Benaglia*, et al.*, 2008).

Recommendations (49-52)

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.	⊕⊕◯◯
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.	⊕◯◯◯
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.	⊕⊕⊕◯
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.	GPP

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 (weak 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 favoured in patients with endometriosis.

From a systematic review including moderate quality evidence, ART was not associated with increased endometriosis recurrence rate. A weak 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.

Research recommendation (R15 – R17)

Studies evaluating IUI and ART should report clinically relevant outcomes (live birth rates and cumulative data), and ideally perform subgroup analysis by stage of endometriosis and type of disease.

Further studies of both medical and surgical treatments for endometriosis-associated infertility are required to clarify the relative effectiveness of treatments, in particular trials comparing ART and IUI to other treatments.

The impact of the extent of disease on the outcome of ART should be further studied, as it could provide data for selection of patients that could benefit from ART.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question III.4).

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III.5. Medical therapies as an adjunct to MAR

PICO Question: Are medical therapies effective as an adjunct to MAR for endometriosis associated infertility?

The role of medically assisted reproduction (MAR) in the treatment of endometriosis-associated infertility is addressed in the previous section and its role is well established. It has been proposed, following numerous non-randomised studies, that medical treatment of endometriosis prior to ART may result in improved outcome, either because of improving oocyte quality or endometrial receptivity. The specific question of GnRH agonist pre-treatment has been addressed in an older Cochrane review (Sallam*, et al.*, 2006) that – based on three included studies in a total of 228 patients – concluded that prolonged downregulation for 3–6 months with a GnRH agonist in women with endometriosis increases the odds of clinical pregnancy by more than 4-fold.

In contrast, the updated version of this Cochrane review (Georgiou*, et al.*, 2019), including 8 parallel-design RCTs involving a total of 640 participants, concluded that the effect of GnRH agonist pre-treatment (for at least 3 months) was very uncertain, both on live birth rate as primary outcome, as well as on secondary outcomes (clinical pregnancy rate, multiple pregnancy rate, miscarriage rate, mean number of oocytes and mean number of embryos). All studies included in this review have compared long-term GnRH agonist versus no pre-treatment. The authors acknowledged the very low quality of data, particularly for reporting live birth rate. Compared to the previous version of the review, the outcome of live birth now includes only one new unpublished trial (NCT01581359) and excludes a previously included RCT (Dicker*, et al.*, 1992) as this paper does not truly report on live birth as per the definition of the international glossary on infertility and fertility care (Georgiou*, et al.*, 2019). For the outcome of clinical pregnancy rate (CPR), the review includes three new RCTs, leading to the results being closer to the line of no effect. Further, subgroup analysis by endometriosis severity highlighted the uncertainty of the effect, and subgroup analysis by previous history of surgery was not possible due to a lack of data.

A more recent RCT investigating the effect of ultralong administration of GnRH agonist, after cauterisation by diathermy of stage I/II endometriosis and before ART, failed to demonstrate a beneficial effect on implantation rate, CPR, or embryo quality (Kaponis*, et al.*, 2020).

A meta-analysis of studies comparing different GnRH agonist protocols (short, long, ultralong) reported that based on evidence from RCTs, a GnRH agonist ultra-long protocol could improve clinical pregnancy rates, especially in patients with stages III/IV endometriosis (RR 2.04, 95%CI 1.37 to 3.04; 2 RCTs; 152 patients). However, when the meta-analysis was performed considering both RCTs and observational studies (n=21), the different down-regulation protocols provided no significant difference in improving clinical outcomes (implantation rate, fertilisation rate, CPR) in patients with endometriosis (Cao*, et al.*, 2020). In a recent randomised open label trial underpowered due to early termination, ultra-long downregulation with a GnRH agonist in previously operated patients with endometriosis compared to classic long agonist protocol failed to improve clinical pregnancy rates in the subsequent initiated fresh ART cycle (Tomassetti*, et al.*, 2021).

Pre-treatment with continuous combined oral contraceptive (OCP) for 6-8 weeks as compared to no pre-treatment before ART was only evaluated in a pilot two-centre trial, that indirectly suggested a potential beneficial effect on CPR (de Ziegler*, et al.*, 2010), however this study was not randomised.

An RCT including 68 women with stage III/IV, administration of dienogest (DNG) during 12 weeks before IVF vs no pre-treatment revealed lower cumulative pregnancy rate and live birth rate in the DNG group

(Tamura, *et al.*, 2019). In a non-inferiority randomised clinical trial including 450 women with stage III/IV randomised to medroxyprogesterone acetate (MPA) + hMG, dydrogesterone + hMG, or progesterone + hMG, the number of oocytes retrieved was higher in the MPA + hMG group but no significant differences in fertilisation or clinical pregnancy rate were observed (Guo, *et al.*, 2020). In a retrospective study including 151 patients with endometriosis and a previous failed IVF cycle, 3 months DNG pre-treatment prior to IVF versus no pre-treatment significantly increased cumulative implantation, clinical pregnancy, and live birth rates (Barra, *et al.*, 2020).

There are no studies comparing the effect of different medical therapies for pre-treatment prior to ART.

Recommendations (53-54)

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.	⊕◯◯◯

There is insufficient evidence to recommend prolonged administration of the COC/progestogens as a pre-treatment to ART to increase live birth rates.	⊕◯◯◯

Justification

Based on the Cochrane review (Georgiou, *et al.*, 2019), 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.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question III.5)

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III.6. Surgical therapies as an adjunct to MAR

PICO Question: Are surgical therapies effective as an adjunct prior to MAR for endometriosis-associated infertility?

It was mentioned (section III.2) that surgery could have a beneficial effect on spontaneous pregnancy rates in women with endometriosis. Thus, one could speculate that surgical treatment of endometriosis prior to treatment with MAR could be effective in improving reproductive outcome.

This section is subdivided into surgical therapy for peritoneal endometriosis, for ovarian endometrioma (ablation, cystectomy, aspiration) and for deep endometriosis prior to MAR.

III.6.a. Surgery prior to MAR in women with peritoneal endometriosis

In a review and meta-analysis of Hamdan *et al.*, 12 studies were included evaluating ART outcomes after surgery for endometriosis. The duration from surgical treatment to ART was not specified in the studies (Hamdan*, et al.*, 2015b). The reviewers stated that the effect of surgery would have been best assessed between women with endometriosis who had received surgical treatment and those who had not received the treatment. However, there was only one study published with this comparison. In a group of 399 women with minimal to mild endometriosis, all visible endometriosis was completely removed prior to ART. In the control group (262 women) only a diagnostic laparoscopy was performed. In the group in which surgery had taken place prior to ART, significant higher implantation, pregnancy, and live birth rates (OR 1.47; 95%CI 1.01 to 2.13) were found. Moreover, the investigators reported a shorter time to first pregnancy and a higher cumulative pregnancy rate after surgical removal of endometriosis prior to ART (Opoien*, et al.*, 2011).

The review by Hamdan *et al.* further included indirect evidence from studies comparing outcomes in women with surgically treated AFS/ASRM stage I/II endometriosis and controls (women with no endometriosis). The reviewers found no difference in the live birth rate (OR 0.88; 95%CI 0.76 to 1.02, 4 studies, 3492 patients), but reported a lower clinical pregnancy rate (OR 0.69; 95%CI 0.50 to 0.96; 9 studies; 4888 patients) and a lower mean number of oocytes retrieved per cycle (mean difference 22.37; 95%CI 23.55 to 21.20; 11 studies; 3909 cycles) in women with surgically treated stage I/II endometriosis (Hamdan*, et al.*, 2015b). In women with stage I/II endometriosis that did not have surgery (or where it was not reported in the study), the review reported no differences in live birth rates, CPR or mean number of oocytes retrieved compared to women without endometriosis.

Recommendations (55)

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.	⊕⊕◯◯

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.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question III.6)

III.6.b. Surgery prior to MAR in women with ovarian endometrioma

Two systematic reviews and meta-analyses have evaluated the impact of endometrioma surgery on ART outcomes. Hamdan *et al*. have observed that surgical treatment of endometrioma before ART had no impact on live birth rate compared to conservative management (5 studies including 655 women) (Hamdan*, et al.*, 2015a). Similarly clinical pregnancy rate, mean number of oocytes retrieved and cancellation rate per cycle did not differ between the two groups. However surgical treatment induced a reduced antral follicle count and required higher dose of FSH for ovarian stimulation suggesting a negative impact on the ovarian reserve.

The second, more recent systematic review and meta-analysis also failed to demonstrate a significant beneficial effect of surgery on live birth rate (OR 1.08; 95%CI 0.80 to 1.45; 7 studies) (Nickkho-Amiry*, et al.*, 2018).

In women who had surgical treatment of one ovary, a lower number of oocytes was retrieved from the surgically treated ovary compared to the contralateral normal ovary without endometrioma in the same patient. (MD 22.59; 95%CI 24.13 to 21.05; 4 studies, 222 cycles). The heterogeneity of data did not allow determining the effect of the size of the endometrioma) (Hamdan*, et al.*, 2015a). The influence of the size of unoperated endometrioma on ART response was evaluated in a prospective study – not included in the review- of 64 women with unilateral endometrioma (Coccia*, et al.*, 2014). A lower number of oocytes were retrieved from the ovary with an endometrioma compared to the healthy contralateral ovary. Endometrioma of ≥30 mm was shown to represent the most important negative factor associated with the total number of follicles and oocytes retrieved.

In a recent retrospective cohort study, ART outcomes were compared in a group of 26 women who underwent 44 ART cycles in the presence of ovarian endometrioma and a surgery group consisting of 53 women who underwent 58 ART cycles after laparoscopic removal of ovarian endometrioma(s). Cystectomy significantly increased the risk of cycle cancellation due to poor ovarian response and/or failed oocyte retrieval 13.7% versus 0%). There was no difference in the live birth rate per embryo transfer in both groups (23.7% versus 26.1%) (Şükür*, et al.*, 2020).

The effect of different surgical techniques has been evaluated only in small studies without showing a clear benefit for a specific approach. A meta-analysis could not be performed due to heterogeneity between groups (Hamdan*, et al.*, 2015a). Cystectomy has the advantage of reducing the risk of recurrence (see chapter IV). A systematic review and meta-analysis evaluating the effect of sclerotherapy has shown a higher number of oocytes retrieved compared with laparoscopic cystectomy, with similar clinical pregnancy rates (Cohen*, et al.*, 2017). A recent retrospective study compared outcomes in 37 women who underwent ethanol sclerotherapy for endometrioma before ART with those in 37 women undergoing ART only. Ethanol sclerotherapy increased the chance of a live birth (OR 2.68; 95%CI 1.13 to 6.36) (Miquel*, et al.*, 2020).

Recommendations (56-57)

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.	⊕⊕◯◯

Surgery for endometrioma prior to ART can be considered to improve endometriosis-associated pain or accessibility of follicles.	GPP

Justification

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.

The clinical evidence and recommendations on surgery for pain in women with ovarian endometrioma are discussed in section II.3.e.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question III.6)

Research recommendation (R18)

RCTs are required to answer the question whether surgery for endometrioma prior to ART improves reproductive outcomes. A proposal for such study has been published (Maheshwari*, et al.*, 2020).

III.6.c. Surgery prior to MAR in women with deep endometriosis

Surgical therapy for deep endometriosis is predominantly performed because of pain rather than infertility, hence randomised studies focusing the direct effect of surgery on the reproductive outcomes of ART are non-existent.

One prospective cohort study in which women with deep endometriosis could choose between surgery prior to ART or ART directly reports higher pregnancy rates after surgery and ART (Bianchi*, et al.*, 2009). However, the numbers of live births did not differ between groups.

A retrospective matched cohort study comparing first-line surgery before ART with first-line ART in patient with colorectal endometriosis-associated endometriosis has observed higher cumulative live birth rates after surgery in the whole study population as well as in women with good ART prognosis (<35 years old, AMH >2 ng/mL and no adenomyosis) as well as in women with AMH serum level <2 ng/mL (Bendifallah*, et al.*, 2017).

Further evidence can be derived from the review by Hamdan, comparing ART outcomes in women with ASRM stage III/IV attempting ART pregnancy after surgery versus women without endometriosis. This indirect evidence showed that women with surgically treated ASRM stage III/IV endometriosis had a lower live birth rate (OR 0.78; 95%CI 0.65 to 0.95; 3 studies; 2550 patients), lower clinical pregnancy rate (OR 0.53; 95%CI 0.33 to 0.84; 6 studies; 3470 patients,) and a lower mean number of oocytes retrieved per cycle (mean difference 22.46; 95%CI 23.42 to 21.51; 8 studies; 3592 cycles) compared to women without endometriosis (Hamdan*, et al.*, 2015b).

Pregnancy and delivery rates after surgery for deep endometriosis in women with previous failed IVF cycles were evaluated in two retrospective studies. In 78 symptomatic infertile women with a mean of 6.6 failed IVF cycles (including frozen cycles), 33 women (42.3%) had a live birth after deep endometriosis surgery (9% naturally and the remaining after ART) (Soriano*, et al.*, 2016). In the second study including 73 infertile women with 2 or more unsuccessful IVF cycles, biochemical pregnancy rate

was 43.8% after resection of endometriosis (83.6% of patients with stage III-IV) with a mean time from surgery to pregnancy of 11.1 months (Breteau*, et al.*, 2020). In that group, 21.8% were natural pregnancies, 71.7% were obtained by ART and 3.1% by intrauterine insemination (data were missing for one patient).

Recommendation (58)

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.	⊕◯◯◯

Justification

From the literature, there is no evidence from randomised 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.

More information on surgery for pain in women with deep endometriosis, risk of surgery and complication rates, is discussed in section II.3.f.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question III.6)

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III.7. Non-medical treatment strategies

PICO QUESTION: WHAT NON-MEDICAL MANAGEMENT STRATEGIES ARE EFFECTIVE FOR INFERTILITY ASSOCIATED WITH ENDOMETRIOSIS ?

Flower *et al.* performed a systematic literature review looking at Chinese medicine post-surgically and were only able to include two studies. This review did not find any improvement in pregnancy rates with the use of Chinese medicine (Flower*, et al.*, 2012).

Zhu *et al.* studied in a three-arm-trial the combination of laparoscopy with oral contraceptives (OCP) versus OCP with herbal medicines versus laparoscopy only. The OCP was administrated for 63 days, herbal medicine for 30 days, with a follow-up period of 14 months for achieving pregnancy (12 months in the laparoscopy-only group). The herbal medicine and/or OCP treatment did not increase the chance of getting pregnant after surgery (pregnancy rates (PR) 30.77% for OCP + herbal medicine, 38.46% for OCP, 46.15% for laparoscopy-only). The authors concluded that it is better to conceive straight after surgery (Zhu*, et al.*, 2014).

In another study by Ding *et al*. Chinese medicine was compared to hormone treatment (12.5mg mifepristone orally every day) for six months with a follow-up of one year. The 80 patients were divided into two different groups “exactly according to the random principle” but is not described in detail. The study did not demonstrate any difference in pregnancy rate (52.5% with Chinese medicine versus 37.5% with hormone treatment) (Ding and Lian, 2015).

Zhao *et al.* included 202 women with endometriosis, laparoscopically and histological verified at six different hospitals in China. The women were randomised through ‘central randomisation’ to either Chinese medicine (CM) mixtures (two different types according to whether the woman was pre-or post-ovulatory) or placebo (with similar dosage, appearance, colour, weight, taste, smell, package and codes compared to CM). Treatment and placebo where started at 1-5 days after surgery. The clinical pregnancy rate (CPR) and live birth rate (LBR) were significant increased in the CM group (LBR: 34,7% (35/101)) compared to placebo (LBR: 20.8% (21/101)). This study is promising, but symptoms such as ‘blood stasis’ and ‘Shen deficiency’ as well as the exact ingredients of the Chinese herbs may be difficult to apply in Western medicine.

Mier-Cabrera *et al.* compared vitamin C and E with placebo and measured oxidative stress markers believed to be linked to fertility. However, there was no increase in the pregnancy rate (Mier-Cabrera*, et al.*, 2008).

All studies but Zhao *et al.* reported no harm, but the definition of “no harm” was seldom described and differed between the studies. Zhao *et al.* described that 48 adverse events occurred in 202 patients, of which 28 in the CM-group. Of these, only five cases of mild diarrhoea and one case of nausea were considered to be related to CM.

Conclusion

Regarding non-medical strategies on infertility, there is no clear evidence that any non-medical interventions for women with endometriosis will be of benefit to increase the chance of pregnancy. 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.

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.

Research recommendation (R19)

Adequately designed trials are needed to define the magnitude of the benefit of non-medical interventions (nutrition, Chinese medicine, electrotherapy, acupuncture, physiotherapy, exercise, and psychological interventions) in endometriosis-associated infertility.

Further research into non-medical interventions for women with endometriosis that employ evidence-based protocols with high intervention integrity is recommended.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question III.7).

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III.8. Fertility Preservation

PICO Question: Is endometriosis an indication for fertility preservation (ovarian tissue / oocytes)?

Patients with severe endometriosis, particularly bilateral endometriomas, are at high risk of premature ovarian insufficiency (POI) and lower AMH levels. Surgical treatment can further impact on ovarian reserve and AMH levels. The relevance of pre-treatment AMH levels to predict the chance of future pregnancy or the need for fertility preservation is unclear, as studies reporting on this have made conflicting conclusions.

A previous ESHRE guideline focusing on fertility preservation, considers that benign diseases could be an indication for fertility preservation, but it does not address whether endometriosis in particular is an indication for fertility preservation. That guideline did state that if AMH levels are measured in women with endometriosis, the levels should be assessed after surgery based on the significant negative impact surgery may have (ESHRE Guideline Group on Female Fertility Preservation*, et al.*, 2020).

A recent large retrospective study by Cobo *et al.* described the outcome of fertility preservation using vitrified oocytes in 485 patients with endometriomas of at least 1cm and an AFC of at least 3 and found oocyte survival rates after warming of 83.2% and a cumulative LBR of 46.4%. This led them to conclude that fertility preservation is a valid treatment option in endometriosis (Cobo*, et al.*, 2020). Of importance is the high rate of women coming back to thaw their gametes (43%), although this does not equal systematically recommending oocyte banking (Somigliana and Vercellini, 2020). This high rate and the short period of time between storing and thawing (mean 1.5 years) suggest that a large proportion of the included women did not undergo proper fertility preservation but, conversely, the oocyte freezing was part of a strategy of infertility treatment (Cobo*, et al.*, 2020). Further, a small retrospective study by Kim *et al.* has shown that the number of oocytes retrieved was significantly lower in the patients with endometrioma undergoing fertility preservation compared with that in infertile patients without endometrioma (5.4 ± 3.8 versus 8.1 ± 4.8) (Kim*, et al.*, 2020).

When ovarian stimulation is not possible or declined by the patient, and surgery is performed for large endometrioma(s), the preservation of ovarian tissue can be an alternative option for fertility preservation, although data in women with endometriosis are scarce (Donnez*, et al.*, 2018).

Recommendation (59)

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.	⊕◯◯◯

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.

For further advice on fertility preservation in women with benign diseases, the ESHRE guideline can be consulted (ESHRE Guideline Group on Female Fertility Preservation*, et al.*, 2020).

Research recommendation (R20)

Studies should focus on identification of women with endometriosis who have higher chances of becoming infertile in the future due to endometriosis or endometriosis surgery (and/or who will need ART anyway). These women may have a true benefit from fertility preservation and this evidence would support a future recommendation supporting fertility preservation in selected women with endometriosis.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question III.8)

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III.9 Impact of endometriosis on pregnancy and pregnancy outcome

NARRATIVE QUESTION: WHAT IS THE IMPACT OF ENDOMETRIOSIS ON PREGNANCY AND OBSTETRIC OUTCOME?

III.9.a. Effect of pregnancy on endometriotic lesions

It is not uncommon for women with endometriosis to be advised that becoming pregnant might be a useful strategy to manage symptoms and reduce disease progression, as 'pseudopregnancy' induced through hormone therapies has a positive effect on symptoms. However, the scanty low/moderate quality data available as reviewed by Leeners *et al*, show that the behaviour of endometriotic lesions during pregnancy seems to be variable, ranging from complete disappearance to increased growth. Although endometriotic lesions in pregnancy may present a decidual reaction similar to changes in the eutopic endometrium, not all endometriotic lesions seem to decidualise during pregnancy as atrophy, fibrosis and necrosis are also possible (Leeners*, et al.*, 2018, Leone Roberti Maggiore*, et al.*, 2016).

The decidualisation of an endometrioma in pregnancy may in some cases resemble malignant ovarian tumours posing a clinical diagnostic dilemma, although the true incidence of this phenomenon is uncertain (prevalence 0-12%, 17 studies reporting 60 cases) (Leone Roberti Maggiore*, et al.*, 2016). First-line management in these cases can be done by serial monitoring (with ultrasound, or MRI if necessary) and expectant management (Leone Roberti Maggiore*, et al.*, 2016). When a malignancy is suspected and surgery is considered necessary, a minimally invasive laparoscopic approach is recommended not later than 23 weeks of pregnancy; these cases should be referred to a tertiary centre with combined experience in gynaecology, oncology, gynaecologic ultrasound, laparoscopic surgery and endometriosis (Leone Roberti Maggiore*, et al.*, 2016).

This led Leeners *et al.* to conclude that pregnancy does not seem to systematically result in benefits for women with endometriosis, and women should not be advised to discontinue periodic evaluations and/or medical treatment after parturition (Leeners*, et al.*, 2018).

Recommendations (60-61)

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.	⊕○○○

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 centre with appropriate expertise.	⊕○○○

Justification

Although this is considered as a narrative question, recommendations were formulated on safety aspects. The first strong recommendation is based on the evidence summarised 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 recognised. As this may lead to surgical intervention and termination of pregnancy, the GDG formulated a recommendation for referral to a centre with expertise.

Research recommendation (R21)
Observational studies should be conducted to assess natural evolution of pre-existing endometrioma or other endometriosis lesions during pregnancy.

III.9.b. Possible complications during pregnancy from a pre-existing endometriosis lesion

III.9.b.1. Endometrioma

Complications deriving from ovarian endometriotic cysts, such as infected, enlarged, and ruptured endometrioma, represent rare events but they should be considered in the differential diagnosis of pelvic pain during pregnancy (Leone Roberti Maggiore*, et al.*, 2016). Conservative and observational management is mostly advisable, although surgery may be necessary in case of acute abdomen due to torsion or cyst rupture (Leone Roberti Maggiore*, et al.*, 2016).

III.9.b.2. Gastrointestinal

Spontaneous intestinal perforation is a serious complication, requiring urgent surgical treatment. It has been hypothesised that extensive decidualisation might weaken the bowel wall, or that adhesions might cause traumas during uterine growth (Leone Roberti Maggiore*, et al.*, 2016, Leone Roberti Maggiore*, et al.*, 2017). During and after pregnancy (mainly in the third trimester) in women with endometriosis, only a small number of cases have been described that were located in the ileum, appendix, caecum, sigmoid and rectum (Glavind*, et al.*, 2018, Leone Roberti Maggiore*, et al.*, 2016). Non-specific symptoms (acute abdominal pain, nausea, and vomiting) were experienced in 94% of the patients (Leone Roberti Maggiore*, et al.*, 2016). Less than half of these cases had a preoperative diagnosis of endometriosis, and continuation of the pregnancy has been feasible (Glavind*, et al.*, 2018).

III.9.b.3. Urinary system

Uro(hemo)peritoneum is very rare: only 2 cases have been reported (Chiodo*, et al.*, 2008, Leone Roberti Maggiore*, et al.*, 2015).

III.9.b.4. Uterus

Spontaneous uterine rupture is also very rare and has been described in 3 cases, all with a history of endometriosis surgery. These ruptures were located in the posterior wall of the uterus at the lower segment level in all cases (Berlac*, et al.*, 2017, Chester and Israfil-Bayli, 2015, Fettback*, et al.*, 2015, Leone Roberti Maggiore*, et al.*, 2016).

III.9.b.5. Vascular: Spontaneous Hemoperitoneum in Pregnancy (SHiP)

Although the aetiology of Spontaneous Hemoperitoneum in Pregnancy (SHiP) is still mysterious, its occurrence seems to be increased in endometriosis. The bleeding arises from pelvic endometriotic implants or ruptured vessels most often situated on the posterior uterine surface or in the parametrium. It occurs mostly in the third trimester of pregnancy (up to 42 days postpartum) and is associated with high maternal and perinatal morbidity/mortality (Leone Roberti Maggiore*, et al.*, 2016, Leone Roberti Maggiore*, et al.*, 2017, Lier*, et al.*, 2017). Neither the stage of endometriosis nor the previous surgical eradication of endometriotic lesions were associated with the severity of SHiP (Lier*, et al.*, 2017). The usual clinical presentation includes acute abdominal pain, hypovolemic shock, and

signs of foetal distress (Leone Roberti Maggiore*, et al.*, 2016, Leone Roberti Maggiore*, et al.*, 2017, Lier*, et al.*, 2017) and leads in approximatively 94,5% of cases to emergency explorative laparotomy mostly combined with Caesarean section (Lier*, et al.*, 2017).

Conclusion

Complications related directly to pre-existing endometriosis lesions are rare, but probably under-reported. Such complications may be related to their decidualisation, adhesion formation/stretching and endometriosis-related chronic inflammation (Leone Roberti Maggiore*, et al.*, 2016). Although rare, they may represent life-threatening situations that may require surgical management.

Research recommendation (R22)

There is a need for prospective, well-designed studies to assess the impact of surgery on subsequent pregnancy evolution, disease phenotype and presence of adenomyosis on the rare complications observed during pregnancy in women with endometriosis.

III.9.c. Impact of endometriosis on early pregnancy (1st trimester)

III.9.c.1. Miscarriage

The systematic review of Leone Roberti Maggiore *et al.* concluded that there was some evidence suggesting a possible association between endometriosis and spontaneous miscarriage, although the important methodological concerns regarding the included studies lead the authors to retain this as a controversial conclusion (Leone Roberti Maggiore*, et al.*, 2016).

After this systematic review, other retrospective studies have been published on the subject with conflicting results.

Santulli *et al.* retrospectively compared previously pregnant women with (284) or without endometriosis (466) and their previous miscarriage rate: this was significantly higher in women with endometriosis compared with the controls (number of pregnancies : 139/478 [29%] versus 187/964 [19%], respectively). The same results were found in a subgroup analysis among women with or without a previous history of infertility (53% versus 30%). Further, they observed that this association was consistent in a sub-analysis for different endometriosis phenotypes (and somewhat higher for cases of superficial endometriosis) (Santulli*, et al.*, 2016).

Kohl Schwartz *at al.*, in a retrospective observational study found a higher miscarriage rate in women with endometriosis (35.8%; 95%CI 29.6% to 42.0%; n=940) compared with disease-free control women (22.0%; 95%CI 16.7% to 27.0%). This difference was significant in the subfertile group women (50.0% [40.7%–59.4%]) vs. (25.8%; 95%CI 8.5% to 41.2%), but no difference appeared in the subgroup of fertile women (24.5%; 95%CI 16.3% to 31.6%) vs. disease-free controls (21.5%; 95%CI 15.9% to 6.8%). The higher miscarriage rate was observed in women with supposed milder forms (rASRM I/II 42.1%; 95%CI 32.6% to 51.4%) (Kohl Schwartz*, et al.*, 2017).

In a large Scottish national population-based cohort study using record linkage to determine pregnancy outcomes in women with endometriosis versus controls, Saraswat at al., analysed a cohort of 14 655 women. On multivariable analysis, after adjusting for age, parity, socio-economic status and year of delivery, the women with endometriosis (86/5375; 1.6%) compared to those without endometriosis (51/8240; 0.6%), presented a significantly higher risk miscarriage with adjusted OR 1.76 (95%CI 1.44 to 2.15)(Saraswat*, et al.*, 2017).

Finally, a more recent systematic review by Horton *et al.* - focusing on the association of adenomyosis and endometriosis with fertility, obstetric, and neonatal outcomes of women through both assisted

reproduction and natural conception, as well as the impact of endometriosis disease subtypes on different stages of the reproductive process -found an increased risk of miscarriage in both adenomyosis and endometriosis (OR 3.40; 95%CI 1.41 to 8.65 and OR 1.30; 95%CI 1.25 to 1.35, respectively) (Horton, *et al.*, 2019).

In conclusion, the data on miscarriage rate in women with endometriosis versus controls are somewhat conflicting, although most studies and systematic reviews observe an increased risk.

III.9.c.2. Ectopic pregnancy

Recently, Yong *et al.*, considering 15 studies in a meta-analysis including both cohort studies and case-control studies, observed, despite the high heterogeneity among studies, a possible evidence of an association between endometriosis and ectopic pregnancy (OR 2.16 to 2.66). There were insufficient data to make any conclusions with respect to anatomic characteristics of endometriosis (e.g., stage) or mode of conception (e.g., ART vs spontaneous) (Yong, *et al.*, 2020).

Recommendation (62)

Clinicians should be aware that there may be an increased risk of first trimester miscarriage and ectopic pregnancy in women with endometriosis.	⊕⊕◯◯

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 (strong recommendation).

Research recommendation (R23)

Larger studies on the evolution of early pregnancy in women with endometriosis versus controls are necessary, particularly with more precise phenotyping including adenomyosis, the role of surgery prior to conception and the mode of conception.

III.9.d. Impact of endometriosis on 2nd and 3rd trimester pregnancy and neonatal outcome

There have been many studies in the literature showing an association between endometriosis and adverse outcome of pregnancy (maternal, foetal and neonatal) that are summarised below, often with conflicting results. The overall low quality of the evidence, its extreme heterogeneity, mixed disease phenotype studied, potential association/confounding with adenomyosis, mixed modes of conception (non-ART and ART), choice of controls and methodology used should lead to a cautious interpretation of these findings (Leone Roberti Maggiore, *et al.*, 2016). A selection of outcomes is discussed below.

III.9.d.1. Gestational diabetes (GDM)

In a systematic review and meta-analysis of 33 studies including 3280488 women, Lalani *et al.* reported higher odds of gestational diabetes (24 studies, OR 1.26; 95%CI 1.03 to 1.55) (Lalani, *et al.*, 2018). On the contrary, a subgroup analysis (natural conceptions and ART pregnancies) could not confirm this association (Lalani, *et al.*, 2018). Taking into account the modest effect sizes, the authors conclude that the findings are difficult to interpret considering the observational nature of included studies. Indeed, other meta-analyses could not confirm this association (Horton, *et al.*, 2019, Leone Roberti Maggiore, *et al.*, 2016, Perez-Lopez, *et al.*, 2018).

III.9.d.2. Preterm birth / premature rupture of membranes

Foetuses and neonates of women with endometriosis were more likely to have premature rupture of membranes (OR 2.33; 95%CI 1.39 to3.90; 7 studies) as well as preterm birth (OR 1.70; 95%CI 1.40 to 2.06; 23 studies) (Lalani, *et al.*, 2018). The latter association was also observed in both women with natural conception and ART (Horton, *et al.*, 2019, Lalani, *et al.*, 2018). Despite these findings, it should be considered that the identified studies are characterised by marked differences in exposure categorisations, analytic approaches, disease phenotypes, potential confounding with adenomyosis, choice of controls and general methodological design, making it difficult to draw definite conclusions (Leone Roberti Maggiore, *et al.*, 2016).

III.9.d.3. Placenta praevia

Compared to women without endometriosis, a higher incidence of placenta praevia has been reported in women with endometriosis, despite the very different study designs employed (OR 3.3; 95%CI 2.37 to 4.63, 18 studies) (Lalani, *et al.*, 2018, Leone Roberti Maggiore, *et al.*, 2016). This association was consistent after subgroup analysis in natural conceptions and ART pregnancies (Lalani, *et al.*, 2018). Horton *et al.* made a similar conclusion (OR 3.09, CI 2.04–4.68, 9 studies) (Horton, *et al.*, 2019). A possible explanation might be the abnormal frequency and amplitude of uterine contractions observed in women with endometriosis, leading to anomalous blastocyst implantation (Kunz, *et al.*, 2000, Leone Roberti Maggiore, *et al.*, 2016).

III.9.d.4. Hypertensive disorders and pre-eclampsia

In a systematic review of 13 studies including 39816 pregnancies with endometriosis diagnosed by biopsy and 2831065 without endometriosis, Perez-Lopez *et al.* did not find any significant difference in the incidence of pre-eclampsia, eclampsia and HELLP syndrome, nor they did any difference in pregnancies achieved spontaneously or by ART (Perez-Lopez, *et al.*, 2018). Leone Roberti Maggiore *et al*. also did not find an association between endometriosis and hypertensive disorders / pre-eclampsia (Leone Roberti Maggiore, *et al.*, 2016). Different results have been reported by Lalani *et al.*, who found pooled results showing higher odds of pre-eclampsia (OR 1.18; 95%CI 1.01 to 1.39; 13 studies), gestational hypertension and/or pre-eclampsia (OR 1.21; 95%CI 1.05 to 1.39 ; 24 studies), without any significant difference between spontaneous and ART pregnancies (Lalani, *et al.*, 2018). Horton *et al.* reported higher odds of pre-eclampsia (OR 1.18; 95%CI 1.03 to 1.36; 11 studies) (Horton, *et al.*, 2019).

III.9.d.5. Stillbirth

Women with endometriosis were more likely to experience stillbirth (OR 1.29; 95%CI 1.10 to 1.52; 7 studies) (Lalani, *et al.*, 2018), The OR for intra-uterine death was similar in the Horton paper (OR 1.25; 95%CI 1.08 to 1.45; 5 studies) (Horton, *et al.*, 2019).

III.9.d.6. Caesarean section

The incidence of Caesarean section was found to be higher in women with endometriosis who become pregnant (OR 1.86; 95%CI 1.51 to 2.29; 6 studies) (Lalani, *et al.*, 2018) possibly due to the higher incidence of malpresentation and labour dystocia observed in these women, as well as the potential influence of previous surgery on the mode of delivery (Lalani, *et al.*, 2018, Leone Roberti Maggiore, *et al.*, 2016). Interestingly, endometriosis was not found to be associated with higher Caesarean section rate in pregnancies achieved by ART (Lalani, *et al.*, 2018). The meta-analysis by Horton *et al.* also reported an increase in Caesarean section rate (OR 1.98; 95%CI 1.64 to 2.38; 10 studies) in studies combining ART and natural conception pregnancies, and in studies reporting only on natural conception (OR 1.82; 95%CI 1.56 to 2.13; 2 studies) (Horton, *et al.*, 2019).

III.9.d.7. Obstetric haemorrhages (placental abruption, ante- and post-partum bleeding)

The systematic review by Leone Roberti Maggiore *et al.* did not observe an increased incidence of placental abruption or ante-partum haemorrhage in women with endometriosis versus controls, Lalani *et al.* found an association between endometriosis and higher risk of ante-partum haemorrhage (OR 1.69; 95%CI 1.38 to 2.07; 5 studies) but not placental abruption (OR 1.46; 95%CI 0.98 to 2.19; 12 studies) (Lalani*, et al.*, 2018, Leone Roberti Maggiore*, et al.*, 2016). The risk of placental abruption was increased in women with endometriosis in the other meta-analysis (OR 1.87; 95%CI 1.65 to 2.13; 8 studies) (Horton*, et al.*, 2019). With regards to post-partum haemorrhage, Lalani *et al.* and Horton *et al.* concluded that the risk is not increased in women with endometriosis (both after natural and in ART conception) (Horton*, et al.*, 2019, Lalani*, et al.*, 2018) .

III.9.d.8. Small for gestational age, admission to NICU, neonatal death

Women with endometriosis were more likely to have babies small for gestational age (SGA) (intra-uterine growth retardation [IUGR] <10th percentile) (OR 1.28; 95%CI 1.11 to 1.49; 19 studies), neonatal death (OR 1.78; 95%CI 1,46 to 2.16; 3 studies), while the only difference of the subgroups of spontaneous vs ART gestations was only in the incidence of neonatal intensive care unit (NICU) admission (OR 0.81; 95%CI 0.28 to 2.36; 1 study) (Lalani*, et al.*, 2018). Some evidence suggestive of endometriosis with IUGR has been described in other systematic reviews (Leone Roberti Maggiore*, et al.*, 2016), while recently Horton *et al.* reported higher odds of neonatal admission following delivery in women with endometriosis (OR 1.29; 95%CI 1.07 to 1.55; 5 studies), but no increased risk of SGA (Horton*, et al.*, 2019).

Recommendation (63)

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.	⊕⊕◯◯

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.

Research recommendation (R24)

Prospective observational studies are needed in pregnant women with endometriosis versus controls to better define obstetric risks for women with endometriosis and the potential usefulness of interventions to prevent them.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question III.9)

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IV. Endometriosis recurrence

Recurrence in endometriosis has been defined as recurrence of pain (dysmenorrhea, dyspareunia, or pelvic pain), as clinical (pelvic fibrotic areas or tender nodules) or radiological detection of recurrent endometriosis lesions, surgically confirmed lesions or as repeat rise of the marker CA-125 after surgery (Ceccaroni*, et al.*, 2019). Recently, recurrence was defined as lesion recurrence on reoperation or imaging after previous complete excision of the disease, with 4 subtypes:

(1) Symptom based suspected recurrence: Symptom recurrence based on patient history, but not proven/confirmed by imaging and/or surgery
(2) Imaging based suspected recurrence: Endometriosis recurrence based on imaging (in patients with or without symptoms).
(3) Laparoscopically proven recurrence: Recurrence of visual endometriosis without histological proof: during laparoscopy endometriosis is visually observed but either not biopsied or biopsied without histologically proven endometriosis.
(4) Histologically proven recurrence: Recurrence of histologically proven endometriosis: during laparoscopy endometriosis is visually observed and confirmed histologically (International working group of AAGL ESGE ESHRE and WES*, et al.*, 2021).

Endometriosis recurrence rates vary widely in the literature, ranging from 0% to 89.6% (Ceccaroni*, et al.*, 2019). This variety can be attributed to different definitions, but also to the length of follow-up, the study design and the sample size, the type and stage of disease, the type of surgery and the postoperative medical treatment (Ceccaroni*, et al.*, 2019).

Risk factors for recurrence include surgery-associated variables (presence and extent of adhesions, radicality of surgery) and patient-related factors (positive family history, lower age at surgery) (Ceccaroni*, et al.*, 2019).

This chapter describes interventions aimed at prevention of recurrence, and the management of recurrent endometriosis.

IV.1 Prevention of recurrence of endometriosis

Interventions for secondary prevention are defined as those aimed at stopping or slowing the progress of the disease after the diagnosis has been established. In the context of this guideline, secondary prevention was defined as prevention of the recurrence of pain symptoms (dysmenorrhea, dyspareunia, non-menstrual pelvic pain) or the recurrence of disease (recurrence of endometriosis lesions documented by ultrasound for ovarian endometrioma or by laparoscopy for all endometriosis lesions) in the long-term (more than 6 months after surgery).

PICO QUESTION: IS THERE A ROLE FOR SECONDARY PREVENTION OF RECURRENCE OF DISEASE AND PAINFUL SYMPTOMS IN PATIENTS TREATED FOR ENDOMETRIOSIS?

IV.1.a. Surgical technique for prevention of recurrence

In women operated on for an endometrioma (≥3 cm), clinicians should perform ovarian cystectomy, instead of drainage and electrocoagulation, for the secondary prevention of endometriosis-associated dysmenorrhea, dyspareunia, and non-menstrual pelvic pain (Hart*, et al.*, 2008, Hart*, et al.*, 2005).

There are currently no studies allowing firm conclusions on the effect on recurrence for different surgical techniques for deep endometriosis .

Recommendation (64)

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.	⊕⊕◯◯

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 favour of cystectomy. Whenever ovarian surgery is performed, the impact on ovarian reserve (i.e., the risk) should be carefully considered against the benefit.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question IV.1)

IV.1.b. Medical therapies for prevention of recurrence

Hormone treatment after surgery aimed at secondary prevention should be distinguished from adjunctive short-term (< 6 months) hormone treatment after surgery aimed at improving the immediate outcomes of surgery. Postoperative adjunctive hormone therapy within 6 months after surgery is discussed in section II.4 Medical therapies adjunct to surgery.

Two aspects are to be considered, the type of medical therapy and the subtype of endometriosis.

IV.1.b.1 Type of medical therapy

In the review by Chen *et al*, data on long-term (13-24 months) pain and disease recurrence are summarised and considered relevant for the assessment of interventions aimed at secondary prevention (Chen*, et al.*, 2020). The review reported uncertainty about the effect of postsurgical medical therapy (GnRH agonists or OCP) on pain recurrence compared to surgery alone (RR 0.70; 95%CI 0.47 to 1.03; 3 RCTs; n=312). With regards to disease recurrence, the review showed that there may be a reduction of disease recurrence in favour of postsurgical hormone therapy (OCP, GnRH agonists, danazol) compared to no postsurgical medical therapy (RR 0.40; 95%CI 0.27 to 0.58; 4 RCTs; n=571).

Another recent review made a similar conclusion (based on similar studies) (Zakhari*, et al.*, 2020), but also conducted an analysis per treatment (OCP, progestin, LNG-IUS and GnRH agonist) suggesting that the OCP had most overall benefit when compared to the other treatments.

Hormonal contraceptives

In the review of Zakhari *et al.*, a subgroup analysis for OCP showed a consistent decreased risk of disease recurrence, compared to controls (RR 0.32; 95%CI 0.23 to 0.44; 6 studies; n=854; fixed effect model). OCP was administered continuously in all but one study (Zakhari*, et al.*, 2020).

A review focusing exclusively on postoperative OCP, showed that in women with surgically treated endometriosis, including ovarian cystectomy if an endometrioma was present, postoperative OCP for 6 to 24 months can be effective for the prevention of endometriosis-associated dysmenorrhea, but not

for non-menstrual pelvic pain or dyspareunia. However, this effect is not sufficiently substantiated if postoperative OCP are used for only 6 months either cyclically (evidence not convincing) or continuously (evidence controversial) (Seracchioli*, et al.*, 2009). Since both continuous and cyclic OCP administration regimens seem to have comparable effects, the choice of regimen can be made according to patient preferences. The protective effect seems to be related to the duration of treatment (Seracchioli*, et al.*, 2009).

Progestogens

In women with moderate to severe dysmenorrhea receiving operative laparoscopy for endometriosis, recurrence of dysmenorrhea was lower in the group with a levonorgestrel-releasing intrauterine system (LNG-IUS) postoperatively than in the control group receiving expectant management (Abou-Setta*, et al.*, 2006, Abou-Setta*, et al.*, 2013).

A more recent meta-analysis on the topic included 7 studies: 4 randomised controlled trials with 212 patients, 1 prospective cohort study with 88 patients, and 2 retrospective studies with 191 patients (Song*, et al.*, 2018). The meta-analysis showed that LNG-IUS was significantly effective in reducing pain after surgery (MD 12.97; 95%CI 5.55 to 20.39), with a comparable effect to GnRH agonist (MD 0.16; 95%CI 2.02 to 1.70). LNG-IUS was also effective in decreasing the (pain and/or disease) recurrence rate (RR 0.40; 95%CI 0.26 to 0.64), with an effect comparable to OCP (OR 1.00; 95%CI 0.25 to 4.02) and danazol (RR 0.30; 95%CI 0.03 to 2.81). Furthermore, patients' satisfaction with LNG-IUS was significantly higher than that with OCP (OR 8.60; 95%CI 1.03 to 71.86). However, vaginal bleeding was significantly higher in the LNG-IUS group than in the gonadotropin-releasing hormone agonist group (RR 27.0; 95%CI 1.71 to 425.36).

A retrospective study comparing postoperative treatment with dienogest (n=130), LNG-IUS (n=72) or no treatment (n=83), confirmed the efficacy of the LNG-IUS for postoperative pain control and prevention of recurrence (6, 12 and 24 months), but could not make a conclusion on the superiority of LNG-IUS compared to dienogest (Lee*, et al.*, 2018).

In the review of Zakhari *et al*, a subgroup analysis for progestogen included a single small study showing a non-significant decreased risk of disease recurrence, compared to controls for (RR 0.17, 95%CI 0.02 to 1.36, 32 patients). (Zakhari*, et al.*, 2020). In a study by Trivedi *et al*, 98 patients suffering from minimal, mild, moderate or severe endometriosis, with or without infertility, who had undergone laparoscopy, were treated with dydrogesterone 10 mg/day (or 20 mg/day in severe cases) orally from day 5 to day 25 of each cycle for 3 to 6 months. Pelvic pain, dysmenorrhea and dyspareunia improved significantly after the first cycle of treatment. By the end of the sixth cycle, the reduction in pelvic pain, dysmenorrhea and dyspareunia was 95%, 87% and 85%, respectively. A total of 21.1% of the patients were considered cured and 66.7% showed improvement (Trivedi*, et al.*, 2007).

GnRH agonists

In the review of Zakhari *et al.*, a subgroup analysis for GnRH agonist reported a significant decreased risk of disease recurrence compared to controls (RR 0.33; 95%CI 0.51 to 0.87; 7 studies; 929 patients) (Zakhari*, et al.*, 2020).

IV.1.b.2 Endometriosis subtype

Although most studies and reviews on postoperative medical therapy evaluated its effect in an unselected population of women with endometriosis, few studies have specifically evaluated the benefit of medical therapies in women surgically treated for endometrioma or deep endometriosis.

Ovarian endometrioma

In a review by Vercellini *et al.*, two studies specifically evaluating the effect of postoperative hormonal contraceptives on endometrioma recurrence were summarised (Vercellini, *et al.*, 2010). Based on the pooled results, the reviewers reported that a recurrent endometrioma developed in 26/250 women who regularly used oral contraceptive postoperatively (10%; 95%CI 7 to 15%) compared with 46/115 who did not use oral contraceptives (40%; 95%CI 31 to 50%), with a common OR of 0.16 (95%CI 0.04 to 0.65) (Seracchioli, *et al.*, 2010, Vercellini, *et al.*, 2008, Vercellini, *et al.*, 2010).

Another review summarised the data for continuous versus cyclic postoperative hormone therapy. In a meta-analysis of 2 studies, they reported endometrioma recurrence in 6/102 women with continuous use versus 12/103 women with cyclic contraceptive use (RR 0.53; 95%CI 0.22 to 1.31) (Muzii, *et al.*, 2016).

Deep endometriosis

Available data about usage of hormone treatments for prevention of deep endometriosis recurrence are less robust whereas long-term administration of postoperative hormone treatments seems to prevent recurrence of endometriosis-associated symptoms (Koga, *et al.*, 2015). The review refers to a single prospective study showing an overall recurrence rate of 7% after surgical management of deep endometriosis in 500 women with a follow-up of 2 to 6 years. The rate of recurrence was lower in women who conceived after surgery and used postpartum progestogens compared to those who had abandoned treatment but did not become pregnant (Donnez and Squifflet, 2010).

Recommendations (65-67)

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.	⊕⊕◯◯

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.	⊕◯◯◯

For the prevention of recurrence of deep endometriosis and associated symptoms, long-term administration of postoperative hormone treatment can be considered.	⊕◯◯◯

Justification

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 favour 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.

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 favour was considered justified, while for deep endometriosis, only a weak recommendation could be formulated.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question IV.1)

IV.1.c. ART and endometriosis recurrence

The available evidence on the impact of ovarian stimulation on the progression of endometriosis or its recurrence was recently summarised in a systematic review (Somigliana*, et al.*, 2019). Based on 4 case reports and 12 observational studies, the review concluded that: ART does not increase the risk of endometriosis recurrence. Based on low to very low-quality evidence and therefore less reliable, the reviewer further reported that (i) the impact of ART on ovarian endometriomas, if present at all, is mild, (ii) IUI may increase the risk of endometriosis recurrence and (iii) deep endometriosis might progress with ovarian stimulation.

Recommendation (68)

Clinicians can perform ART in women with deep endometriosis, as it does not seem to increase endometriosis recurrence per se.	⊕⊕⊕○

Justification

From a systematic review including moderate quality evidence, ART was not associated with an increased endometriosis recurrence rate, and therefore should not be withheld from women with endometriosis requiring ART to achieve pregnancy. Patients with endometriosis can be reassured regarding the safety of ART.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question IV.1)

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IV.2 Treatment of recurrent endometriosis

PICO Question: How should patients with reoccurring endometriosis OR recurring symptoms be managed? Is repetitive surgery effective for symptoms associated with endometriosis?

IV.2.a. Medical treatment for recurrent endometriosis

Medical treatment of recurrent endometriosis after surgery has been described in few RCTs and uncontrolled observational studies.

In an RCT, 242 women with recurrent pelvic pain within 1 year following laparoscopic surgery were randomised to dienogest or depot leuprolide acetate. VAS scores for pelvic pain, back pain, dyspareunia or endometrioma size were significantly lower at 12 weeks follow-up, but there was no difference between the 2 treatments for any of these outcomes. Dienogest and depot leuprolide acetate showed a different side effect profile; fewer hot flushes and vaginal dryness with dienogest, less vaginal bleeding and weight gain with leuprolide acetate (Abdou*, et al.*, 2018).

Another RCT compared 6-month treatment with desogestrel or OCP in 40 women with recurrent dysmenorrhea and/or pelvic pain after conservative surgery. Both treatments resulted in a significant decrease of VAS scores at 6 months compared to baseline. There was no difference between the treatments with regards to efficacy. Breakthrough bleeding was more often reported with desogestrel, while weight gain was reported with OCP (Razzi*, et al.*, 2007).

In the RCT by Vercellini and colleagues, 90 women with recurrent moderate or severe pelvic pain after conservative surgery for symptomatic endometriosis, were randomised to 6-month treatment with cyproterone acetate or a continuous monophasic OCP (Vercellini*, et al.*, 2002). The study showed no difference in efficacy for cyproterone acetate versus a continuous monophasic OCP. In both groups, about 70% of patients were satisfied with the treatment.

In the study of Koshiba *et al*, dienogest treatment immediately after recurrence was effective in controlling disease progression. The study consisted of a small cohort of 11 patients with endometrioma recurrence that received dienogest, of which 7 patients were followed up for 24 months and in four of them (57.1%) complete resolution of recurrent endometrioma was achieved (Koshiba*, et al.*, 2018).

In the study from Lee *et al.*, 121 women with surgically confirmed endometriosis and previous cystectomy were treated with dienogest (2 mg) at detection of recurrence of symptoms (dysmenorrhea or pelvic pain) (n=33) or disease (n=88) (new endometrioma of minimum 2cm) (Lee*, et al.*, 2018). Dienogest was effective in reducing the size of endometriomas (2.74 ± 1.53 at 24 weeks versus 3.77 ± 1.59 at baseline) and for symptomatic relief (VAS score 2.32 ± 0.95 at 24 weeks versus 5.01 ± 1.71 at baseline). Medical treatment for recurrent symptoms after medical treatment was described by Hornstein *et al*. In a trial, 36 women with recurring endometriosis symptoms after 3 or 6 months nafarelin treatment were retreated with nafarelin (200µg twice daily for 3 months). The study reported improvements for dysmenorrhea, pelvic pain, tenderness, induration, and dyspareunia. Symptoms worsened after the end of the 3 months nafarelin treatment, but dysmenorrhea and pelvic tenderness remained improved compared to the start of retreatment (Hornstein*, et al.*, 1997).

IV.2.b. Surgical treatment of recurrent endometriosis

To our knowledge, there are no studies reporting on the efficacy and safety of surgical treatment for recurrent endometriosis apart from one small, uncontrolled study. In the study by Candiani *et al.* surgery for recurrent endometriosis was performed in 42 women (Candiani*, et al.*, 1991). During a mean follow-up 41.8 ± 30.3 months, recurrence of dysmenorrhea and pelvic pain were reported in 8 (19%) and 7 (17%) of the women, respectively. A third surgery was performed in 6 (14%) women after reappearance of symptoms or clinical signs. The study did not include a control group, and some patients received pre- or postoperative medical treatment.

Specifically for endometrioma, a small prospective study (n=11) showed that surgery for recurrent endometriomas is more harmful to healthy ovarian tissue and ovarian reserve than first surgery as demonstrated by removal of larger ovarian tissue at histology and a trend towards lower AFC (3.5 ± 1.4 after second surgery vs 5.1 ± 2.8 after the first surgery) at follow-up (3 months after surgery) (Muzii*, et al.*, 2015).

Recommendation (68)

Any hormone treatment or surgery can be offered to treat recurring pain symptoms in women with endometriosis	⊕◯◯◯

Justification

Recurrence of endometriosis is a prevalent clinical observation, but yet, evidence specifically addressing are scarce and direct evidence of efficacy is only available for GnRH agonists and dienogest. While acknowledging the lack of evidence, it should not be considered directive towards prioritizing certain treatments over others that have been shown effective in relieving endometriosis-associated pain. Therefore, the GDG recommends that any hormone treatment or surgery could be offered. The benefits, risks and side effects of the different hormone and surgical treatments are discussed in sections II.2 and II.3, respectively (Healey*, et al.*, 2010).

Even if treatment options are available, other causes for the pain symptoms symptoms such as adenomyosis or pelvic floor dysfunction should be investigated, particularly if the recurrence of symptoms occurs soon after surgery..

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question IV.2)

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V. Endometriosis and adolescence

Limited evidence is available about endometriosis and adolescence. There are no large epidemiologic studies on endometriosis among adolescents.

Dysmenorrhoea is a very common phenomenon in adolescents. In different studies, the incidence of endometriosis in adolescents (defined as girls and young women under the age of 20 years) with chronic pelvic pain is reported to be ranging from 25-73% (Brosens, *et al.*, 2013, Shah and Missmer, 2011). The true disease prevalence in the general adolescent population remains unknown.

As in adults, the pathophysiology of endometriosis in adolescents is largely unknown. Endometriosis has been described not only in post-menarcheal girls, possibly resulting of retrograde menstruation, but also in prepubertal but post-thelarcheal girls, suggesting multifactorial peripubertal aetiologies of the disease in the adolescent population (Shah and Missmer, 2011).

In this chapter, the evidence concerning diagnostic and treatment procedures of endometriosis specific for adolescents is summarised.

V.1. Diagnosis

PICO Question: Which diagnostic procedures should be applied in adolescents with possible endometriosis?

V.1.a. Diagnostic process

In adults, the time between onset of symptoms and diagnosing endometriosis is reported to be approximately 7 years when onset of disease was in adults and more than 12 years if onset of disease was in adolescence (Geysenbergh, *et al.*, 2017). The diagnostic process in adolescents may be more complex and the awareness of endometriosis in adolescents in medical professionals and caregivers of adolescents is low. Greene and co-workers showed in a study about the diagnostic experience among 4334 women with surgically confirmed endometriosis that women who first experienced symptoms as adolescents waited three times as long as those with symptoms first as adults (6 vs 2 years, $p<0.0001$), it took longer before a diagnosis was made (5.4 vs 1.9 years, $p<0.0001$), and they were not taken seriously (65.2% vs 48.9%, OR 1.95, 95%CI 1.69 to 2.24) or told that nothing was wrong (69.6% vs 49.8%, OR 2.26, 95%CI 1.97 to 2,59) more often than women experiencing first symptoms as adults (Greene, *et al.*, 2009).

V.1.b. Risk factors for adolescent endometriosis

Conflicting results regarding family history, genital malformations, and age at menarche as risk factors for adolescents to develop endometriosis have been described . A positive family history for endometriosis may (Shah and Missmer, 2011) or may not (Vicino, *et al.*, 2010) be associated with adolescent endometriosis, genital malformations leading to outflow obstructions may (Yang, *et al.*, 2012) or may not (Vicino, *et al.*, 2010) be present more often in adolescents with endometriosis, and early age of menarche may (Brosens, *et al.*, 2013, Geysenbergh, *et al.*, 2017, Treloar, *et al.*, 2010) or may not (Chapron, *et al.*, 2011) increase the risk of adolescent endometriosis.

Geysenbergh and co-workers conducted a systematic review to develop a questionnaire in order to identify adolescents at risk to develop endometriosis. From five studies using questionnaires for identifying adult women with endometriosis, six questions were selected to predict the presence of endometriosis in adolescents. These questions were: age at menarche (earlier age at menarche is associated with greater incidence of endometriosis when comparing age at menarche of <10 to 12 years, 95%CI 1.0 to 1.8; p value test for trend <0.001); cycle length (higher incidence of endometriosis in case of shorter cycle length during adolescence comparing cycle length <26 to 26-31 days (95%CI 1.1 to 1.5); presence of dysmenorrhea; type of pelvic pain; presence of menstrual dyschezia; presence of dysuria. The authors state that this questionnaire should be pilot-tested and validated in a large population-based sample before it can be used for screening (Geysenbergh, *et al.*, 2017). In a study aimed at finding risk factors for deep endometriosis, Chapron and co-workers investigated 229 women with histologically confirmed endometriosis. They found that the following factors, present in adolescence, were more frequent in women with deep endometriosis as compared to women with superficial or ovarian endometriosis: a positive family history for endometriosis (p=0.02), non-contraceptive use of oral contraceptives (p=0.001), and absenteeism from school (p=0.04) (Chapron, *et al.*, 2011).

Recommendations (70-71)

In adolescents, clinicians should take a careful history to identify possible risk factors for endometriosis, such as a positive family history, obstructive genital malformations, early menarche, or short menstrual cycle.	⊕◯◯◯

Clinicians may consider endometriosis in young women presenting with (cyclical) absenteeism from school, or with use of oral contraceptives for treatment of dysmenorrhea.	⊕◯◯◯

Justification

In adolescents, even more than in adults, there is a long way from onset of symptoms to a diagnosis of endometriosis To facilitate diagnosis or at least further investigation, studies have examined risk factors and signs in adolescents. Knowledge of these risk factors and signs in adolescents could facilitate the diagnostic process and is therefore strongly recommended.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question V.1).

V.1.c. Clinical symptoms

Unlike in adults, in whom diagnosis can be made based on pain or infertility, adolescents are most often diagnosed based on pain symptoms only.

Some authors state that adolescent endometriosis may be distinct from adult endometriosis. It has been speculated that endometriosis in adolescents may be more progressive than endometriosis in adults, and that clinical presentation of endometriosis in adolescents has a more varying pattern as compared to the presentation in adults. This assumption may be corroborated by the findings reported in a retrospective questionnaire study in over 4000 women with surgically confirmed endometriosis. Women with onset of symptoms during adolescence more frequently reported other symptoms over their lifetime compared to onset of symptoms as adults: having menstrual pain in combination with

ovulatory as well as non-menstrual pain (71.7% vs 58.3%), heavy bleeding (63.5% vs 49.3%), premenstrual spotting (37.2% vs 29.3%), bowel symptoms (99.4% vs 97.5%) and systemic symptoms including nausea/stomach upset or dizziness/headache during menses (55.2% vs 34.0%; p<0.0001 for all) (Greene*, et al.*, 2009).

DiVasta and co-workers asked adults (n=107) and adolescents (n=295) with endometriosis about their endometriosis-related symptoms. No differences between adolescents and adults in severity of menstrual pain, taking medication for pain, and experiencing only some relief from hormone treatment for pain were reported. There were no differences between adults and adolescents in urinary and bowel symptoms. Adolescents more often experienced pain from menarche (p=0.002) than adults although this may be influenced by recall bias. Both adults and adolescents experienced general pelvic pain. Adolescents experienced nausea with their pain more often than adults (p=0.004). From this study it was concluded that dysmenorrhea and acyclic general pelvic pain are common symptoms of endometriosis in adults as well as in adolescents, and that nausea in combination with pelvic pain should perhaps be considered a marker to raise suspicion for endometriosis in adolescents (DiVasta*, et al.*, 2018). Results of a study in which early menstrual characteristics in women diagnosed with endometriosis were investigated, showed that early dysmenorrhea may be a risk factor or an early sign of endometriosis (Treloar*, et al.*, 2010). In a small retrospective study among Italian adolescents with surgically confirmed endometriosis (n=38), all reported having chronic pelvic pain (Vicino*, et al.*, 2010). However, in a retrospective study among 65 Chinese adolescents in whom endometriosis was surgically confirmed, only 13/65 (20.6%) had chronic pelvic pain, whereas 45 women (69.2%) had cyclic pelvic pain. 19 women (29.2%) had acute abdominal pain, gastrointestinal symptoms (n=19, 29.2%), irregular menses (n=5, 7.7%), and dyspareunia (n=1, 1.5%) (Yang*, et al.*, 2012). In conclusion, whereas in adults dysmenorrhea is one of the leading symptoms, there may be a more varied clinical presentation of endometriosis in adolescents.

Recommendation (72)

In adolescents, clinicians should take a careful history and consider the following symptoms as suggestive of the presence of endometriosis: - chronic or acyclical pelvic pain, particularly combined with nausea, dysmenorrhea, dyschezia, dysuria, dyspareunia - cyclical pelvic pain.	⊕○○○

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.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question V.1)

V.1.d. Clinical examination

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.

Recommendation (73)

In the absence of evidence for adolescents specifically, the recommendations for clinical examination in adults can be applied.

- Clinical examination, including vaginal examination where appropriate, should be considered to identify deep nodules or endometriomas in patients with suspected endometriosis, although the diagnostic accuracy is low.
- In women with suspected endometriosis, further diagnostic steps, including imaging, should be considered even if the clinical examination is normal.

The GDG decided to formulate an additional good practice point clarifying specific considerations in adolescents.

The GDG recommends that before performing vaginal examination and/or rectal examination in adolescents, the acceptability should be discussed with the adolescent and her caregiver, taking into consideration the patient's age and cultural background.	GPP

V.1.e. Imaging

Transvaginal ultrasound is a well-accepted diagnostic tool especially for ovarian endometriosis in adult women, but in adolescents, especially in adolescents with an intact hymen, transvaginal ultrasound should only be carried out after careful consideration with the patient and her caregiver. Alternatives for transvaginal ultrasound may be transabdominal, transperineal or transrectal ultrasound. Based on the age and cultural background of the adolescent, the most appropriate method must be selected.

In their study about Chinese adolescents with endometriosis, Yang and co-workers found a pelvic mass on ultrasound in 87.3% of women, indicating that ultrasound is a reliable method of diagnosing endometriosis in adolescents, but it was not clear whether transvaginal or transabdominal ultrasound was used (Yang, *et al.*, 2012). Martire and co-workers conducted transvaginal or transrectal ultrasound in 270 adolescents having menstrual bleeding problems, endometriosis related symptoms or no symptoms at all. 13% of these had signs of endometriosis (signs of ovarian endometriosis 61%, adenomyosis 44%, deep endometriosis 28%, and indirect signs of adnexal adhesions 50%). The authors conclude that transvaginal and transrectal ultrasound can be used as a non-invasive diagnostic test of endometriosis in adolescents (Martire, *et al.*, 2020). Brosens and co-workers suggest that transvaginal hydrolaparoscopy may be helpful and less invasive than conventional diagnostic laparoscopy for diagnosing endometriosis in adolescents (Brosens, *et al.*, 2013). However, transvaginal hydrolaparoscopy is not widely used.

Recommendation (74)

Transvaginal ultrasound is recommended to be used in adolescents in whom it is appropriate, as it is effective in diagnosing ovarian endometriosis. If a transvaginal scan is not appropriate, MRI, transabdominal, transperineal, or transrectal scan may be considered.	⊕⊕◯◯

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 favour) (Nisenblat, *et al.*, 2016).

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.

Further information
Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question V.1).

V.1.f. Laboratory parameters

The usefulness of laboratory parameters in diagnosing endometriomas in adolescents was tested in a retrospective chart review in 267 women with endometriomas and 235 women with other benign adnexal cysts. Although significant differences were found in haemoglobin levels, platelets, platelet-to-lymphocyte ratio (PLR), platelet crit (PCT) and CA-125 between adolescents with endometrioma and adolescents with other benign cysts, the authors conclude that these parameters showed low diagnostic performance for detecting endometriomas with AUC (Seckin*, et al.*, 2018). In a study with 147 adolescents with surgically confirmed endometriosis and 10 controls, CA125 levels did not discriminate between cases and controls. Moreover, CA125 levels did not correlate with different pain types and severity (Sasamoto*, et al.*, 2020).

Recommendation (75)

Serum biomarkers (e.g., CA-125) are not recommended for diagnosing or ruling out endometriosis in adolescents.	⊕⊕⊕○

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).

Further information
Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question V.1)

V.1.f. Diagnostic laparoscopy

Using diagnostic laparoscopy, endometriosis in adolescents may look different from adult endometriosis. In adolescents, there may be a predominance of atypical red or clear lesions as compared to adults (summarised by (Shah and Missmer, 2011)). In a review of 12 studies about the description of endometriotic lesions using r-AFS classification, differences between adults and adolescents are the presence of red, vesicular implants and the rarity of deep (>5 mm) or adenomyotic type of endometriosis in adolescents. Moreover, progression of disease in the adolescent seems to be primarily characterised by extensive adhesions and endometrioma formation (Brosens*, et al.*, 2013). In a retrospective clinical study of 38 women ≤ 21 years of age with surgically confirmed endometriosis, laparoscopic findings were: stage I: n=7 (18.4%), stage II: n=5 (13.2%), stage III: n=13 (34.2%), stage IV: n=13 (34.2%). Ovarian endometriosis was present in 40.6%, peritoneal in 29.7% and ovarian plus peritoneal in 29.7% (Vicino*, et al.*, 2010). In a retrospective analysis of 63 adolescents with endometriosis, 7.9% of women was diagnosed having stage I, 3.2% having stage II, 52.4% having stage III, and 36.5% having stage IV endometriosis (Yang*, et al.*, 2012). All rAFS stages of endometriosis can

be present in adolescents, as well as peritoneal, ovarian, and deep endometriosis, although the presence of deep endometriosis may be less frequent in adolescents.

Recommendation (76)

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.	⊕⊕◯◯

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 (weak 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.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question IV.1)

V.1.g. Histology

PICO Question: Should diagnosis of endometriosis in adolescents be confirmed by histology?

In a systematic review, 15 articles were assessed in which in total 880 adolescents (defined as aged between 10 and 21 years, but within this range different age groups were included) underwent a laparoscopy (Janssen*, et al.*, 2013). Main symptoms leading to laparoscopic investigation in adolescents were chronic pelvic pain (CPP), CPP not responding to NSAIDs or oral contraceptives, or dysmenorrhea. The overall prevalence of endometriosis visually confirmed at laparoscopy in all patients in all studies was 62% (543/880; range 25-100%). In girls with CPP resistant to treatment the prevalence was 75% (237/314), in girls with dysmenorrhea the prevalence was 70% (102/146) and in girls with CPP not resistant to treatment the prevalence was 49% (204/420). These differences between the subgroups were not statistically significant due to the large heterogeneity of studies.

Other studies included in the Janssen *et al*. review used different classification systems. Considering the ASRM classification, 50% of adolescents (175/349) had minimal endometriosis, 27% (69/259) had mild endometriosis, 18% (47/259) had moderate endometriosis and 14% (35/259) had severe endometriosis(Janssen*, et al.*, 2013). The overall prevalence of ASRM classified moderate to severe endometriosis was 32% (82/259) in all girls, 16% (17/108) in girls with CPP resistant to treatment, 29% (21/74) in girls with dysmenorrhea and 57% (44/77) in girls with CPP. The authors concluded that nearly two-thirds of adolescents with CPP or dysmenorrhea had laparoscopic evidence of endometriosis, including moderate to severe disease in approximately one-third of those having endometriosis.

The histological analysis of endometriosis biopsies was not documented or performed in 33% (5/15) of studies (Janssen*, et al.*, 2013). If documented, histological confirmation rate was 93% (221/239), varying

between 43 and 100% in the different studies. The authors advised to treat adolescents with dysmenorrhea or CPP with an NSAID, if necessary, in combination with hormonal contraceptives. If pain persists after three to six months, they stated that a definitive diagnosis was recommended, and a laparoscopy was indicated to diagnose or exclude endometriosis.

Recommendation (77)

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.	⊕⊕◯◯

Justification

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.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question V.1b)

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V.2. Treatment

PICO Question: What is the best treatment for adolescents with (suspected) endometriosis?

V.2.a Medical treatment

High quality evidence about the efficacy of medical treatment of endometriosis in adolescents is scarce. The efficacy of NSAIDs or other analgesics in adolescents with endometriosis-related pain is not well established, because clinical studies have mostly been conducted in adult women.

In a randomised double-blind placebo-controlled study, 76 adolescents with moderate to severe dysmenorrhea were randomised between ethinylestradiol 20µg/levonorgestrel 100µg (OCP) and placebo. OCP users reported a lower score (less pain) on the Moos Menstrual Distress Score (mean score 3.1 ± 3.2 versus 5.8 ± 4.5; 95 CI difference 0.88-4.53), lower worst pain (p=0.02) and a lower analgesic use (p=0.05) after three months compared to the placebo group (Davis*, et al.*, 2005).

Yoost and co-workers investigated the effect on pain of the levonorgestrel containing intra uterine system (LNG-IUS). In a small retrospective chart study of 14 adolescents with histologically proven endometriosis, they showed that 13 experienced resolution of pain in the months after positioning the LNG-IUS. The results of this study have to be interpreted with caution, because almost all participants were using other hormone medication together with the LNG-IUS to suppress endometriosis-related pain symptoms (Yoost*, et al.*, 2013).

In a prospective open label study in 97 adolescents with clinically suspected or surgically confirmed endometriosis, the effect of dienogest on pain scores using the visual analogue scale (VAS), quality of life measured with EHP-30 and lumbar spine bone mineral density (BMD) after one year were investigated. Mean VAS at baseline was 64.3 mm (SD 19.1 mm). After 24 weeks of treatment, the mean VAS score was 9.0 mm (SD 13.9 mm) and 81% of participants experienced a reduction in VAS of ≥30%. EHP-30 scores improved in all items assessed. Lumbar spine BMD decreased 1.2% (SD 2.3%) after one year, but partially recovered after six months. The authors concluded that dienogest is as effective for endometriosis-associated pain in adolescents as in adults, but the need for tailored treatment in the adolescent population is important (Ebert*, et al.*, 2017).

Gonadotropin Releasing Hormone (GnRH) agonists are frequently used in adults having endometriosis related pain. Because of its wide range of short-term side effects including mood swings, hot flushes, weight gain, and long-term side effects, for example probably partly irreversible effects on BMD, they are predominantly prescribed after first line of hormone treatment has failed. As adolescents are in the critical time window for the attainment of peak bone mass, it is particularly important to address this effect on BMD if GnRH agonists are considered for use in adolescents. In a number of articles, the group of Gallagher and co-workers have reported about their investigations on the effectiveness and safety of GnRH agonists in adolescents. In a randomised, double-blind placebo-controlled trial, 50 adolescents with surgically confirmed endometriosis were treated for one year with GnRH agonists 11.25 mg/three months. Most of the participants had been treated with other hormone medication before. They were randomised between add-back therapy consisting of norethindrone acetate 5 mg daily (NA) plus conjugated equine estrogens 0.625 mg daily (CEE) (combined add-back group), or NA plus placebo (progestogen add back group). Quality of Life (QoL) was assessed using the SF-36, Menopause Rating Scale (MRS) and Beck Depression Inventory II (BDI). After one year of treatment, QoL was improved in both groups as compared to baseline, whereas adolescents using GnRH agonists and combined add-back had a better QoL than adolescents using GnRH agonists with add-back of NA only. Scores on MRS and BSI did not change (Gallagher*, et al.*, 2017).

The same group showed in a similar study design in 65 adolescents that after 12 months total body bone mineral content and BMD had increased in the NA plus CEE group (bone mineral content +37g, p<0.001 and BMD +0.012 g/cm2, p=0.05), but not in those receiving NA plus placebo (bone mineral content p=0.19 and BMD p=0.95) (DiVasta*, et al.*, 2015). This suggests that with regard to BMD, GnRH agonists use is safe as long as add-back therapy is provided, preferably combined.

Finally, a retrospective follow-up study was undertaken in the same study group, aimed at identifying short term, long term, and irreversible side effects. Of 51 women who had been treated with GnRH agonists with the two different regimens of add-back (NA plus CEE or NA plus placebo) during their adolescence, 25 responded to the questionnaire. 96% reported short term side effects (during treatment); 80% reported long term side effects (lasting > 6 months after stopping treatment), and 45% reported side effects they considered irreversible, including memory loss, insomnia, and hot flashes. 48% of adolescent women rated GnRH agonists plus add-back as the most effective hormone medication for treating endometriosis pain. More subjects who received a combined add-back regimen versus standard one drug add-back would recommend GnRH agonists to others and felt it was the most effective hormone medication (Gallagher*, et al.*, 2018).

Recommendations (78-81)

In adolescents with severe dysmenorrhea and/or endometriosis-associated pain, clinicians should prescribe hormonal contraceptives or progestogens (systemically or via LNG-IUS) as first line hormone therapy because they may be effective and safe. However, it is important to note that some progestogens may decrease bone mineral density.	⊕◯◯◯
The GDG recommends clinicians consider NSAIDs as treatment for endometriosis-associated pain in adolescents with (suspected) endometriosis, especially if first line hormone treatment is not an option.	GPP
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.	⊕⊕◯◯
The GDG recommends that in young women and adolescents, 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.	GPP

Justification

Studies on the medical treatment of endometriosis-associated pain are mostly performed in adults. In adolescents, we summarised 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 (weak 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.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question V.2)

V.2.b Surgical treatment

In two studies, symptom relief after surgery was described as well as recurrence of symptoms (Roman, 2010, Yeung*, et al.*, 2011). In a prospective observational case series, 17 adolescents with rASRM stage I-III endometriosis underwent complete laparoscopic excision of all present endometriosis. Dysmenorrhea, dyschezia, constipation, tender examination, painful exercise, intestinal cramping, and bladder pain decreased significantly after surgical treatment. After a follow-up period of in average 23.1 months (max 66 months), 8/17 (47.1%) had a subsequent laparoscopy for persistent pain, but in none of these patients endometriosis was found visually or histologically at repeat laparoscopy (Yeung*, et al.*, 2011). Lower numbers of recurrent symptoms were found in a comparative cohort study of 20 adolescents with rASRM stage I to IV endometriosis undergoing electrical excision of endometriosis (all patients), and additional ovarian cystectomy (2/20 patients, 10%). Dysmenorrhea and pelvic pain symptoms decreased significantly and quality of life increased after surgery. 2/20 (10%) adolescents underwent a second laparoscopy because of pain within two years after first surgical treatment, but no recurrent endometriosis was found (Roman, 2010).

In two other studies there was a focus on recurrence of endometriosis, but not on initial symptom relief after surgery (Lee*, et al.*, 2017, Tandoi*, et al.*, 2011). In a study of Lee and co-workers, recurrence after laparoscopic ovarian endometriosis cyst enucleation was investigated. Recurrence was defined as the sonographic presence of a cyst mass ≥20 mm after initial surgery. After follow-up of 47.3 (±44.3; 3-161) months, 17 (16.2%) adolescents had a cyst recurrence. Based on individual preference, some adolescents used OCP or GnRH agonist after surgery, with a mean duration of 5.5 (± 1.6) months. The use of postoperative hormone suppression therapy was not a risk factor for recurrence, and no other risk factors were identified(Lee*, et al.*, 2017). Recurrence rates, defined as endometriosis related symptoms or ultrasound diagnosis of ovarian or pelvic endometriosis after initial surgery, were reported in a retrospective cohort study of Tandoi *et al*. Fifty-seven adolescents (rASRM I/II 14 (24%), rASRM stage III/IV 43 (76%)) underwent conservative laparoscopic or laparotomic surgery for endometriosis and had a follow-up of at least five years. 32 adolescents experienced a recurrence (56%, 95%CI 43 to 68%). Part of the adolescents used OCP after surgery: 27 (47%) did not use OCP, 14 (25%) used OCP during less than 12 months, 16 (28%) longer than 12 months. No risk factors for recurrence were identified (Tandoi*, et al.*, 2011).

Recommendations (82-83)

In adolescents with endometriosis, clinicians may consider surgical removal of endometriosis lesions to manage endometriosis-related symptoms. However, symptom recurrence rates may be considerable, especially when surgery is not followed by hormone treatment.	⊕◯◯◯

The GDG recommends that if surgical treatment is indicated in adolescents with endometriosis, it should be performed laparoscopically by an experienced surgeon, and, if possible, complete laparoscopic removal of all present endometriosis should be performed.	GPP

Justification

Only small studies providing low quality evidence were identified about surgical treatment of endometriosis in adolescents, therefore the results have to be interpreted with caution (Lee*, et al.*, 2017, Roman, 2010, Tandoi*, et al.*, 2011, Yeung*, et al.*, 2011). The studies summarised evidence with regards to the relief of painful symptoms, but also on the recurrence rates. Overall, based on limited data, laparoscopy seems to be temporarily beneficial for pain relief. However, in a decision to proceed to surgery, the risks of surgery and postoperative complications, and considerable recurrence rates should be considered against the relative benefit of surgical treatment.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question V.2)

V.2.c Combined medical and surgical treatment.

Seo *et al.* studied the effect of long-term treatment with GnRH agonists and OCP after conservative surgery for endometriosis in 34 adolescents. In this retrospective cohort study, adolescents underwent adhesiolysis, stripping and enucleation of ovarian cysts, excision of concurrent deep endometriosis and fulguration of peritoneal endometriosis. Post-surgery, patients were treated with GnRH agonists for 5.4 ± 1.2 months and subsequently with OCP during 47.9 ± 29.3 months. Recurrence, defined as sonographically observed presence of ovarian cysts ≥2 cm, was present in 2/34 (5.8%) of adolescents after a median of 41 (6-159) months (Seo*, et al.*, 2017).

Doyle and co-workers investigated how endometriosis rASRM stages developed in time in a population of 90 adolescents with rASRM stages I/III. They had persistent endometriosis symptoms after medical treatment for endometriosis and therefore underwent laparoscopy including lesion destruction by CO_2 laser or electrocautery and adhesiolysis. After surgical treatment adolescents were treated by OCP (82/90, 91%), progestogen (11/90, 12%) and/or GnRH agonists plus add-back (70/90, 78%). A second laparoscopy was performed because of increasing pain despite medical treatment after 29 (6-112) months. In 63 adolescents (70%), the same rASRM stage was found, in 17 (19%), the rASRM stage improved one stage, in 1 (1%) rASRM improved two stages, and in 9 (10%), rASRM stage worsened one stage. The authors concluded that after combined surgical and hormone treatment, progression of disease may be retarded in adolescents. However, in this study all adolescents underwent a second laparoscopy because of increasing pain symptoms despite the use of hormone treatment (Doyle*, et al.*, 2009).

Recommendation (84)

In adolescents with endometriosis, clinicians should consider postoperative hormone therapy, as this may suppress recurrence of symptoms.	⊕◯◯◯

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 favour of postoperative hormone therapy was formulated.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question V.2).

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V.3. Fertility preservation

PICO QUESTION: IS ENDOMETRIOSIS IN ADOLESCENTS AN INDICATION FOR FERTILITY PRESERVATION (OVARIAN TISSUE /OOCYTES) ?

There is a lack of robust evidence concerning the usefulness of fertility preservation in women with endometriosis, let alone adolescents with endometriosis. Data about women with endometriosis who actually underwent fertility preservation are very scarce. Women with endometriosis may benefit from fertility preservation as they have an increased risk of premature ovarian exhaustion, and approximately half of them will face subfertility.

In opinion papers by Somigliana *et al.* and by Carillo *et al.*, it was speculated that for those with bilateral ovarian endometriomas and those operated unilaterally with a contralateral recurrence, fertility preservation may be particularly indicated (Carrillo*, et al.*, 2016, Somigliana*, et al.*, 2015). The role of a woman's age needs specific attention, as young women may have a larger risk of recurrence, and they are more likely to postpone pregnancy. In younger women, it is expected that the quality of the banked oocytes or ovarian fragments will be higher than in older women (Somigliana*, et al.*, 2015).

In a large retrospective cohort study, 485 out of 1044 (46.5%) women with endometriosis who had vitrified oocytes returned for fertility treatment. Their mean age was 35.7 ± 3.7 years, they had 7.1 ± 6.5 retrieved oocytes per cycle, and storage time was 1.7 ± 0.4 years. Cumulative live birth rate (CLBR) per patient was 46.4%. It was statistically higher in women ≤ 35 years of age as compared to women > 35 years. Women ≤ 35 years who had not undergone ovarian surgery before fertility preservation had a higher CLBR than women who underwent unilateral surgery and women who underwent bilateral surgery, respectively. In women older than 35 years, surgery had no influence on CLBR. Based on these results, the authors suggest that fertility preservation may be beneficial for women with endometriosis and that if fertility preservation is considered in young women with endometriosis, it should be done before ovarian surgery is carried out (Cobo*, et al.*, 2020).

Clinical, logistic, and financial aspects need to be further investigated before fertility preservation can be advised for adolescents with endometriosis.

Recommendations (85-86)

The GDG recommends that adolescents with endometriosis are informed of the potential detrimental effect of ovarian endometriosis and surgery on ovarian reserve and future fertility.	GPP

Fertility preservation options exist and the GDG recommends that adolescents are informed about them, although the true benefit, safety, and indications in adolescents with endometriosis remain unknown.	GPP

Justification

There are no studies evaluating the efficacy, or relevance of fertility preservation, namely oocyte cryopreservation, in adolescents with endometriosis. Data in adults are scarce as well (see section III.8). Still, clinicians can discuss fertility preservation in selected patients, such as those at risk of ovarian damage, which can include, but are not limited to, those with bilateral ovarian endometriomas or those with unilaterally operated endometrioma with a contralateral recurrence. Individual counselling may be offered taking into account age, risk of premature ovarian insufficiency because of the presence of

endometriomas per se or because of surgery, and the success rates and risks of fertility preservation. If fertility preservation is carried out in young women (≤35 years), it is suggested that fertility preservation precedes ovarian surgery. However, until now it is unclear how to identify women who will benefit from fertility preservation to render oocyte vitrification cost beneficial.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question V.3)

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VI. Endometriosis and menopause

Due to the steroid-dependent nature of the disease, most women with endometriosis experience regression of disease after menopause. Still, a number of women experience endometriosis-related symptoms after natural or surgical menopause (i.e., after bilateral oophorectomy). Additionally, women with a history of endometriosis may experience worsening of symptoms and reactivation of residual disease with the use of hormone therapies aimed at relieving postmenopausal complaints.

This chapter explores the connection between endometriosis and menopause, discussing whether endometriosis can still be active after menopause and whether women with a history of endometriosis are at higher risk of experiencing menopause-related major health concerns. Furthermore, the treatment of postmenopausal symptoms in women with a history of endometriosis, and surgical treatment of endometriosis in postmenopausal women are discussed.

VI.1. Endometriosis in postmenopausal women

NARRATIVE QUESTION: IS ENDOMETRIOSIS STILL ACTIVE AFTER MENOPAUSE?

There exist only very scarce data on the prevalence of endometriosis after menopause. In four narrative reviews, the incidence of endometriosis in postmenopausal women was estimated to range from 2-5% (Bendon and Becker, 2012, Oxholm*, et al.*, 2007, Polyzos*, et al.*, 2011, Streuli*, et al.*, 2017), referring primarily to three, very old articles (Henriksen, 1955, Punnonen*, et al.*, 1980, Ranney, 1971). A more recent retrospective cohort study also described a 4% prevalence of postmenopausal endometriosis (Matalliotakis*, et al.*, 2019). Because endometriosis is a steroid dependent disease, menopausal hormone therapy (MHT) is believed to stimulate the growth of endometriosis, especially estrogen-only therapies, although it is also described in women receiving combined MHT (Gemmell*, et al.*, 2017). However, endometriosis has also been reported in postmenopausal women who do not use hormone therapy, which underlines the complex pathogenesis of this disease. Whether this is a result of extra-ovarian estrogen production (e.g., skin, fat tissue etc.) or lesion-specific production of estrogen due to local overexpression of aromatase and other steroidogenic genes and proteins is currently unclear (Attar and Bulun, 2006, Noble*, et al.*, 1996).

Conclusion

Clinicians should be aware that endometriosis can still be active/symptomatic after menopause.

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VI.2. Treatment of endometriosis in postmenopausal women

Regarding treatment of symptoms in postmenopausal women one should keep in mind the potential increased risk of underlying malignancy in this population and the uncertainty of the diagnosis, as pain symptoms may present differently in this group of women compared to premenopausal women.

PICO Question: Is surgical treatment effective and safe in women with a history of endometriosis?

One should keep in mind the potential risk of underlying malignancy and the uncertainty of the diagnosis when postmenopausal women present with (chronic) pelvic pain. Hormone therapy approaches are more limited compared to premenopausal women due to the low systemic estrogen levels. Therefore, in review articles on this subject, it is suggested that first line treatment for endometriosis in postmenopausal patients should be surgical (Oxholm*, et al.*, 2007, Pavone and Bulun, 2012, Polyzos*, et al.*, 2011). Also, there are very little options available for medical treatment - besides using analgesics or aromatase inhibitors (see below) - due to the naturally low levels of estrogen in postmenopausal women.

VI.2.a. Surgical treatment

We identified five cohort studies on surgery in postmenopausal endometriosis patients: three studies described a cohort of postmenopausal women who presented with pain and subsequently underwent surgery whilst two retrospective cohort studies reported on women in whom endometriosis was identified based on histology.

VI.2.a.1. Efficacy of surgery in postmenopausal women

A prospective cohort by Redwine *et al.* included 75 women with previous bilateral salpingo-oophorectomy (BSO) who received excision of histologically confirmed endometriosis as treatment for pain (Redwine, 1994). The control group consisted of women with biopsy-proven endometriosis who did not have previous BSO, hysterectomy or ovarian remnant syndrome. Women treated surgically for endometriosis following BSO were significantly older (37.8 ± 8.1 versus 31.3 ± 6.9 years; p<0.001) and tended to have intestinal involvement (risk ratio 2.3, 95%CI 1.5 to 3.5). Most women had a marked alleviation of pain after excision of endometriosis, although only 13 patients underwent a re-operation due to pelvic pain. No malignancy was found in this study.

Behera *et al.* described a retrospective cohort of 124 women with chronic pelvic pain after hysterectomy and BSO (Behera*, et al.*, 2006). They all underwent laparoscopy and if any abnormalities were visualised, they were resected. The most common histopathologic findings included adhesions (in 94% of patients), adnexal remnants (26%), and endometriosis (15%). Laparoscopic treatment of any pelvic pathologic condition improved pain symptoms in the majority of women (58.9%) (follow-up of less than one to six years). In 2 women (1.4%) a malignancy of the bowel was found.

Clayton *et al.* described a case series of five women with recurrent pain after BSO and hysterectomy who had residual endometriosis managed by laparoscopic excision (Clayton*, et al.*, 1999). Four of the women had bowel endometriosis. Immunohistochemistry showed positive immunoreactivity for estrogen and progesterone receptors in all patients, suggesting that the endometriosis was active and responsive to exogenous estrogen. The women had improved pain symptoms at 4 months after surgery (one patient was lost to follow-up).

VI.2.a.2. Risk of malignant transformation in postmenopausal women

Consideration of the possibility of malignancy should be taken in postmenopausal women with endometriosis irrespective of symptoms. This may require transvaginal ultrasound scan or MRI or further imaging studies and/or the surgical exploration of the area.

A retrospective cohort study identified 72 postmenopausal patients with histologically confirmed endometriosis, of which 57 had endometriomas (Morotti*, et al.*, 2012). In 35% of these endometriomas a (pre)malignancy was found. Only 14 women (16.7%) had a previously known history of endometriosis. The indications for surgery were ovarian cyst (31 patients, 43.0 %), ovarian or endometrial (pre)cancer (25 patients, 35 %), or other, mostly benign indications. In none of the women pain was the indication for surgery.

Sun *et al.* described a retrospective cohort study of postmenopausal patients in whom endometriosis was histologically confirmed (Sun*, et al.*, 2013). Of these 69 women, 45 (65%) were referred with an abdominal mass without symptoms, only 8 women presented with abdominal pain. In 62 women an endometrioma was found and 10 women (14%) had a coexisting ovarian, endometrial, or cervical malignancy.

In conclusion, there is not enough data to accurately estimate the risk of malignancy in postmenopausal women with a history of endometriosis, as data are mainly based on surgically-induced menopause. Women after natural menopause are generally older, and consequently their general risk of malignancy will be higher. The risk of malignancy in (premenopausal) women with endometriosis is covered in Chapter X (Endometriosis and Cancer).

Recommendations (87-88)

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.	⊕◯◯◯

The GDG recommends that clinicians 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.	GPP

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 (weak 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.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question VI.2)

VI.2.b. Medical treatment

In cases where surgery is not feasible, or symptoms persist or recur after surgery, medical treatment of endometriosis-associated symptoms may be indicated. However, similar to surgery, there is very little data on medical treatment for endometriosis in postmenopausal women.

Estrogen is considered to be one of the predominant drivers of endometriotic growth. As such, in postmenopausal women on MHT, one of the first therapeutic steps should be to discontinue MHT whilst considering the likely recurrence of menopausal vasomotor symptoms.

Theoretically, aromatase inhibitors (AIs) are able to block extraovarian estrogen production which is the main estrogen source for postmenopausal women. In addition, P450 aromatase - the central enzyme converting androgens into estrone and estradiol - appears to be overexpressed in endometriotic tissue, although no data are available in tissue from postmenopausal women (Pavone and Bulun, 2012).AIs have been shown effective to reduce endometriosis-associated pain in premenopausal women with severe endometriosis (see also section II.2.e). Specifically in postmenopausal women`, only case reports on treatment with AIs are available. Two reviews describe six case reports to date, which mention that the administration of an AIs for 4-18 months improved pain and reduced the size of endometriotic lesions (Pavone and Bulun, 2012, Polyzos*, et al.*, 2011). One patient reported hot flushes and in one case AI-associated bone loss after nine months of treatment with anastrozole was reported. Although data are very limited, AIs represent a medical alternative to surgery for the treatment of postmenopausal endometriosis.

Recommendation (89)

For postmenopausal women with endometriosis-associated pain, clinicians may consider aromatase inhibitors as a treatment option especially if surgery is not feasible.	⊕◯◯◯

Justification

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 (weak recommendation).

Research recommendation (R25)

More evidence is needed on the efficacy and safety (bone health) of aromatase inhibitors or other medical treatments in postmenopausal women with endometriosis-related pain symptoms.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question VI.2)

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VI.3. Menopausal symptoms in women with a history of endometriosis

PICO Question: Is hormone treatment effective and safe for relief of menopausal symptoms in women with a history of endometriosis?

This chapter evaluates whether hormone replacement treatment (HRT), now called menopausal hormone therapy (MHT), in postmenopausal women with a history of endometriosis is effective and safe. Efficacy is assessed by the impact of treatment on menopausal symptoms and menopause-related quality of life, while safety is assessed by the risk of recurrence of disease or associated symptoms, and incidence of cancer. A distinction is made between natural and surgical menopause.

VI.3.a. MHT for menopausal symptoms in women with a history of endometriosis

No studies were available specifically evaluating the efficacy of MHT in reducing menopausal symptoms or improving menopause-related quality of life in women with a history of endometriosis. Deduced from the recommendations for postmenopausal women in general, as summarised by the International Menopause Society (IMS), North American Menopause Society (NAMS) and the European Menopause and Andropause Society (EMAS), MHT is considered the most effective therapy for vasomotor symptoms and urogenital atrophy, with possible beneficial effects on other menopause-related complaints and quality of life (Baber*, et al.*, 2016, The ESHRE Guideline Group on POI*, et al.*, 2016).

VI.3.b. MHT and recurrence of endometriosis in women after natural menopause

Although the literature search included women with endometriosis after both surgical menopause and natural menopause, no evidence could be retrieved on the latter. The recommendations on surgical menopause could be extrapolated to women with endometriosis and natural menopause, bearing in mind the differences between both patient groups (e.g., age, gradual vs. abrupt onset of menopausal symptoms).

VI.3.c. MHT and recurrence of endometriosis in women after surgical menopause

The management of menopause in women with a history of endometriosis has been summarised in a systematic review, which included only two randomised trials and 4 observational studies (Gemmell*, et al.*, 2017), all focusing on patients after surgically-induced menopause (Fedele*, et al.*, 1999, Matorras*, et al.*, 2002).

The systematic review concluded, consistently with an older Cochrane review (Al Kadri*, et al.*, 2009), that there appeared to be a small association between the treatment with MHT and recurrence of endometriosis, although none of the studies found a statistically significant difference between treatment and control groups. In the RCT of Matorras *et al.*, 115 patients received continuous transdermal estrogen plus cyclical oral progesterone, and 57 received no hormone treatment. After 45 months, 4 of the patients in the treated arm and none in the non-treated arm reported recurrence of pain. The authors found recurrence of the endometriosis in two of these four patients with recurrent pain and these two patients had to be re-operated (Matorras*, et al.*, 2002). Based on 13 case reports and case series, the review counted 17 cases of recurrent endometriosis in postmenopausal women taking some form of MHT (Gemmell*, et al.*, 2017). However, lack of information about the completeness of surgery limits the interpretation of these findings. Indeed, persistent macroscopic implants following

surgery are more likely associated to a recurrence of pain if stimulated by a cyclical administration of combined estrogen-progestogen regime.

VI.3.d. MHT and risk of malignancy

The systematic review by Gemmell *et al.* performed an extensive search on the topic of malignancy. Regarding the risks of treatment with MHT in women with a history of endometriosis they found a few case reports of malignancy, mostly in women who received estrogen-only MHT. In this systematic review they reported a total of 25 patients with malignant transformation of endometriotic lesions from case reports and case series. Nineteen of these 25 women received unopposed estrogens. Although data are very scarce and regarded as low quality, it seems advisable to consider using continuous combined estrogen-progestogen or tibolone regimes in women requiring MHT over unopposed estrogen (Gemmell*, et al.*, 2017).

VI.3.e. Regimen of MHT in women with a history of endometriosis

Evidence is limited with regards to the regimen of MHT in women with endometriosis (Baber*, et al.*, 2016). Considering responsiveness of ectopic endometrial tissue to sex steroids, it seems advisable to use continuous estrogen-progestogen in those patients requiring MHT, in order to limit any abnormal estrogen-induced endometriosis proliferation in persistent endometriosis tissue.

Tibolone could be an alternative for combined MHT as this molecule has a typically estrogenic effect on vasomotor symptoms and bone, yet a progestogenic-like effect on the endometrium. In a small RCT, 10 women received continuous transdermal estrogen plus cyclical oral progestogen, and 11 women were randomised to tibolone. After 12 months, 4 patients in the first group and 1 in the second experienced moderate pelvic pain (Fedele*, et al.*, 1999). The authors concluded that Tibolone might be a safe alternative for combined MHT. Additionally, one case report described a woman with recurrent disease after using tibolone (Sundar*, et al.*, 2007). More recent evidence shows a higher risk of endometrial carcinoma than combined MHT, therefore this is not recommended as a first choice MHT treatment (Løkkegaard and Mørch, 2018).

Phytoestrogens are non-steroidal plant-derived compounds, structurally similar to endogenous estrogens, but capable of showing both estrogenic and antiestrogenic effects. Among these, soy isoflavone supplements are commonly seen as a safer alternative to MHT, particularly in women with estrogen-dependent conditions (Chen*, et al.*, 2019). Evidence from published human trials reveals that soy isoflavone treatment does not stimulate proliferation in the endometrium during short-term treatment for at least 2 years (North American Menopause Society, 2011). Endometrial safety in long-term users is unknown. The effect of isoflavone supplement in postmenopausal women with endometriosis has not been properly investigated. Notably, one case report showed that five-year use of a highly concentrated isoflavone supplement was associated with florid recurrence of endometriosis and ureteral malignant Müllerian carcinosarcoma (Noel*, et al.*, 2006). This report raises further concerns over the use of phytoestrogens in postmenopausal women with a history of endometriosis (Cotroneo and Lamartiniere, 2001), despite some clinical and animal literature suggesting a reduced risk of endometriosis with dietary isoflavones (Tsuchiya*, et al.*, 2007, Yavuz*, et al.*, 2007).

Recommendations (90-92)

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.	⊕⊕◯◯
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	⊕⊕◯◯
The GDG recommends that clinicians 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.	GPP

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 summarised 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 (weak 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).

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question VI.3)

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VI.4. Menopause-related major health concerns in women with endometriosis

NARRATIVE QUESTION: ARE WOMEN WITH ENDOMETRIOSIS AT HIGHER RISK OF EXPERIENCING MENOPAUSE-RELATED MAJOR HEALTH CONCERNS?

Oophorectomy is an important, widely used treatment for endometriosis. Women with endometriosis are therefore more likely to undergo oophorectomy than women in the general population and also to undergo this surgery at a much younger age. The resulting surgically induced early menopause increases the risk of diminished bone density or osteoporosis (Farmer, *et al.*, 2003) and dementia (Georgakis, *et al.*, 2019), but also could have an effect on other menopause-related major health concerns.

A recent review based on an extensive search of articles on the associations between endometriosis and other chronic diseases, concluded that endometriosis patients have a higher risk of developing asthma, some auto-immune diseases and cardiovascular disease (Shigesi, *et al.*, 2019). For this chapter we focused on the menopause-related major health concerns, thus on the higher risk of cardiovascular disease.

Two large prospective cohort studies have been published on this subject. Mu *et al.* described a subgroup of the Nurses' health study II with laparoscopically confirmed endometriosis, which prospectively included around 5,000 women and compared them to 100,000 women without endometriosis (Mu, *et al.*, 2016). They found a significantly higher risk of myocardial infarction (RR 1.52), angina (RR 1.91), coronary surgery (RR 1.35) or any of these coronary heart disease endpoints combined (RR 1.62) in women with a history of endometriosis. These higher risks were independent of demographic, family history, reproductive and lifestyle confounders. 42% of the association between endometriosis and coronary heart disease could be explained by a history of hysterectomy/BSO and earlier age at surgery. In the same cohort of women, they also found a higher risk for developing hypercholesterolemia (RR 1.25) and for hypertension (RR 1.14) (Mu, *et al.*, 2017).

Conclusion

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.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question VI.4)

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VII. Extrapelvic Endometriosis

VII.1. Diagnosis

PICO Question: How reliable is imaging for diagnosing extrapelvic endometriosis?

VII.1.a. Abdominal wall, umbilical, perineal and inguinal endometriosis

Abdominal wall endometriosis is frequently associated with a gynaecologic procedure such as Caesarean section, laparoscopy, or abdominal hysterectomy (Andres, *et al.*, 2020, Chamie, *et al.*, 2018, Hirata, *et al.*, 2020, Horton, *et al.*, 2008). In a review of 445 cases, the pooled mean time interval between index surgery and clinical presentation of abdominal wall endometriosis was 3.6 years (Horton, *et al.*, 2008).

Caesarean section scar endometriosis is the most common abdominal wall endometriotic lesion and is located near or at the site of the surgical incision. It is estimated to occur in 0.03%–1.5% of women after Caesarean delivery (Chamie, *et al.*, 2018, Hirata, *et al.*, 2020). Umbilical endometriosis is rare, estimated to occur in 0.5%–1.0% of all cases of endometriosis (Chamie, *et al.*, 2018, Hirata, *et al.*, 2020). Episiotomy endometriosis is even less common and is estimated to occur in 0.01%–0.06% of women after episiotomy (Chamie, *et al.*, 2018, Hirata, *et al.*, 2020).

Scar endometriosis may be identified at transabdominal ultrasonography (TAS), computed tomography (CT), and magnetic resonance imaging (MRI) in patients who are symptomatic or asymptomatic (Chamie, *et al.*, 2018, Hirata, *et al.*, 2020, Yarmish, *et al.*, 2017).

The appearance of scar endometriosis at ultrasound, CT, or MRI depends on the phase of the patient's menstrual cycle, the chronicity of the process, the number of stromal and glandular elements, and the amount of bleeding and associated inflammation (Chamie, *et al.*, 2018, Gidwaney, *et al.*, 2012, Yarmish, *et al.*, 2017).

TAS is usually the first imaging examination performed to evaluate focal abdominal or inguinal wall thickening identified at clinical examination. TAS depicts the extent and nature of such focal lesions and is useful for establishing or excluding abdominal wall hernia (Gidwaney, *et al.*, 2012).

In women with a palpable anterior abdominal or pelvic wall abnormality, CT findings may help diagnose, exclude, or suggest the presence of a mass and define its extent and nature. CT may be performed with or without intravenous contrast material, although the use of contrast material improves its sensitivity and specificity (Chamie, *et al.*, 2018, Gidwaney, *et al.*, 2012, Yarmish, *et al.*, 2017). The highest reported combined sensitivity of CT imaging for the diagnosis of abdominal wall endometriosis is (0.69; 95%CI 0.48 to 0.86) and specificity (0.97; 95% CI 0.91 to 1.00) (Yarmish, *et al.*, 2017)

In younger patients, MRI is preferred because of its improved tissue characterisation and lack of ionizing radiation. CT and MRI may be used to diagnose or exclude alternative diagnoses in the anterior abdominal and pelvic wall, including hernia, abscess, hematoma from other causes, and other soft-tissue tumours (Chamie, *et al.*, 2018, Gidwaney, *et al.*, 2012, Yarmish, *et al.*, 2017).

Recently, for the diagnosis of umbilical endometriosis sensitivity of 87.1% for physical examination, 76.5% for transabdominal ultrasonography, 75.6% for CT, and 81.8% for MRI was reported (Hirata, *et al.*, 2020).

VII.1.b. Thoracic endometriosis

Diagnosis of thoracic endometriosis syndrome (TES) is usually based on clinical grounds. Symptoms have a catamenial (cyclical) pattern, occurring between 24h before and 72h after the onset of menses, and typically recurring (Andres, *et al.*, 2020, Johnson, 2004, Rousset, *et al.*, 2014).

Thoracic endometriosis syndrome includes five well-recognised clinical entities grouped into two forms, namely the pleural form with catamenial pneumothorax, non-catamenial endometriosis-related pneumothorax, catamenial haemothorax, and the pulmonary form with catamenial haemoptysis and lung nodules (Joseph and Sahn, 1996, Rousset, *et al.*, 2014, Vigueras Smith, *et al.*, 2020).

Catamenial pneumothorax is defined by at least two episodes of pneumothorax occurring during this time interval. In a review of Gil and co-workers, data on 490 cases of catamenial pneumothorax were summarised. Pneumothorax was mainly present in the right lung (456 of 490 cases, 93%) (Gil and Tulandi, 2019). The right-side predominance of symptoms represents a diagnostic clue (Johnson, 2004, Rousset, *et al.*, 2014). Diaphragmatic endometriosis and/or nodules (as visualised by laparoscopy) were observed in 265 of 297 cases (89%) (Gil and Tulandi, 2019).

TES is the term used to refer to the various clinical and radiological manifestations resulting from the presence and cyclical changes of functional endometrial tissue in a thoracic structure (visceral or parietal pleura, lung parenchyma, airways, or diaphragm) (Johnson, 2004, Rousset, *et al.*, 2014). Approximately 90% of patients with thoracic endometriosis syndrome experience catamenial thoracic pain and different entities may be associated . The right hemithorax is involved in more than 90% of all forms (Johnson, 2004, Rousset, *et al.*, 2014).

In a recent systematic review only one study with 33 patients with diaphragmatic endometriosis evaluated the accuracy of MRI for the diagnosis of this condition. This study reported a sensitivity of 83% for MRI when using fat-suppressed T1-weighted sequences for the diagnosis of diaphragmatic endometriosis (Andres, *et al.*, 2020).

Recommendations (93-94)

Clinicians should be aware of symptoms of extrapelvic endometriosis, such as cyclical shoulder pain, cyclical spontaneous pneumothorax, cyclical cough, or nodules which enlarge during menses.	GPP

It is advisable to discuss diagnosis and management of extrapelvic endometriosis in a multidisciplinary team in a centre with sufficient expertise.	GPP

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.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question VII.1)

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VII.2. Treatment

PICO Question: Does treatment for extrapelvic endometriosis relieve symptoms ?

VII.2.a. Extrapelvic endometriosis of the abdominal wall, the umbilicus, and the inguinal region

Treatment of extrapelvic endometriosis of the abdominal wall, the umbilicus or the inguinal region will depend on the location of the lesions. If complete excision is possible, this is the treatment of choice; when this is not possible, long-term medical treatment is necessary (Andres*, et al.*, 2020, Keckstein*, et al.*, 2020, Veeraswamy*, et al.*, 2010). The principles of medical treatment for pelvic endometriosis will similarly apply for extragenital endometriosis (Hirata*, et al.*, 2020).

Abdominal wall and perineal endometriosis are usually treated by complete excision of the nodule (Liang*, et al.*, 1996, Marinis*, et al.*, 2006, Nissotakis*, et al.*, 2010, Song*, et al.*, 2011). Recurrence after resection was 4.3% in an earlier mentioned review of 445 cases of abdominal wall endometriosis (Horton*, et al.*, 2008).

According to Zhu and co-workers there is no difference between the pain relief among patients with abdominal wall endometriosis treated with ultrasound-guided (high-intensity focussed ultrasound) HIFU and surgical excision. The hospital stay was shorter in the HIFU group than in the surgery group. Change in the size of nodules was more remarkable in the group treated with surgery (Zhu*, et al.*, 2017).

For umbilical endometriosis, a similar approach can be applied taking into account cosmetic consequences (Hirata*, et al.*, 2020, Keckstein*, et al.*, 2020). The cumulative recurrence rate was 1.34% at 6 months, 6.35% at 12 months, and 6.35% at 60 months after surgery performed for umbilical endometriosis. Medical treatment can be advised for the conservative therapy of umbilical endometriosis, the efficacy of oral progestins, gonadotropin-releasing hormone agonists, and oral contraceptives was 91.7%, 81.8%, and 57.1%, respectively (Hirata*, et al.*, 2020).

In endometriosis of the inguinal region, the proximity to neural structures and femoral vessels should be considered and a multidisciplinary approach is advised (Hirata*, et al.*, 2020).

VII.2.b. Thoracic and diaphragmatic endometriosis

Hormone treatment (OCP or GnRH agonist) has been shown to be effective in a significant proportion of patients, although with high recurrence rates. In cases of recurrent pneumothorax or haemothorax, chemical pleurodesis, pleural abrasion or pleurectomy may be helpful (Gil and Tulandi, 2019, Joseph and Sahn, 1996). Persistent haemoptysis due to parenchymal lesions may be treated by lobectomy or segmentectomy (Gil and Tulandi, 2019, Nezhat*, et al.*, 2014).

If diaphragmatic endometriosis is found as the reason for catamenial pneumothorax, consideration should be given to investigation and treatment of pelvic endometriosis. (Ceccaroni*, et al.*, 2013, Gil and Tulandi, 2019, Vigueras Smith*, et al.*, 2020).

According to recent meta-analysis by Ciriaco *et al.* on the treatment of thoracic endometriosis syndrome, video-assisted thoracoscopy (VATS) was the preferred surgical technique (84%; 95%CI 66 to 96) (Ciriaco*, et al.*, 2020). Intraoperative evaluation revealed the presence of diaphragmatic anomalies in 84% of cases (95%CI 73 to 93). The overall pooled prevalence of concomitant or staged laparoscopy was 52% (95%CI 18 to 85). Postoperative hormone therapy was heterogeneous with a pooled

prevalence of 61% (95%CI 33 to 86). Recurrence of symptoms was documented in 27% of patients (95%CI 20 to 34).

When a patient does not want to undergo thoracic surgery or only incomplete resection is expected, in case of catamenial pneumothorax, a bilateral salpingo-oophorectomy (BSO) may be considered in absence of future fertility plans (Keckstein*, et al.*, 2020).

Recommendations (95-96)

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.	⊕◯◯◯

For thoracic endometriosis, hormone treatment can be offered. If surgery is indicated, it should be performed in a multidisciplinary manner involving a thoracic surgeon and/or other relevant specialists.	⊕◯◯◯

Justification

Due to the lack of unequivocal evidence regarding the treatment of extrapelvic endometriosis, clinicians may consider surgical removal of symptomatic extrapelvic endometriosis, when possible, to relieve symptoms. Both for abdominal and thoracic endometriosis, a weak recommendation was formulated.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question VII.2)

Research recommendation (R26)

Prospective studies are needed in the field of extrapelvic endometriosis, especially thoracic endometriosis.

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VIII. Asymptomatic endometriosis

Asymptomatic endometriosis is defined as the incidental finding of peritoneal, ovarian, or deep endometriosis without pelvic pain and/or infertility. Incidental findings of endometriosis have been reported during different gynaecologic procedures (sterilisation, ovarian drilling for PCOS, appendectomy) and examinations (e.g., fertility work-up or general gynaecologic examinations). The exact prevalence of asymptomatic peritoneal endometriosis is unknown, but the presence of endometriosis has been reported in 3 to 45% of women undergoing laparoscopic tubal ligation (Gylfason, *et al.*, 2010, Rawson, 1991). It is unclear, however, whether these women were entirely asymptomatic.

VIII.1. Treatment

PICO Question: Is treatment beneficial for incidental finding of asymptomatic endometriosis?

By definition, patients with an incidental finding of endometriosis do not have symptoms of the disease that require treatment. Treatment could however be indicated to prevent progression of endometriosis.

In this respect, it has been shown that the risk that asymptomatic minimal disease will become symptomatic is low (Moen and Stokstad, 2002).

To date no clinical trials have been performed to assess whether surgery is beneficial compared to expectant management. Furthermore, as with any surgical procedure, surgical excision or ablation has associated risks, such as damage to adjacent anatomical structures. Therefore, surgical treatment for an incidental finding of asymptomatic endometriosis cannot be recommended.

In the absence of evidence of disease progression, medical treatment cannot be recommended either for asymptomatic disease.

Recommendations (97-99)

The GDG recommends that clinicians should inform and counsel women about any incidental finding of endometriosis.	GPP
The GDG recommends that clinicians should not routinely perform surgical excision/ablation for an incidental finding of asymptomatic endometriosis at the time of surgery.	GPP
Clinicians should not prescribe medical treatment in women with incidental finding of endometriosis.	⊕⊕◯◯

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.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question VIII.1)

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VIII.2. Monitoring

PICO Question: Is long term monitoring of women with asymptomatic endometriosis beneficial in preventing adverse outcomes?

The only rationale for long term monitoring of patients with asymptomatic endometriosis would be to prevent the progression of disease and development of symptoms and to avoid a potential malignant transformation.

The conservative management of ovarian masses which have appearances consistent with endometrioma on ultrasound in asymptomatic premenopausal women is a safe option of treatment after proper counselling (Alcazar*, et al.*, 2005).

However, in view of other possible negative consequences of endometriosis (e.g., effects on fertility, increased risk of ovarian malignancy), there is a need for RCTs to determine whether surgery or long-term monitoring should be recommended in asymptomatic patients (Maouris, 1991, Pearce*, et al.*, 2012).

A recent prospective study reported that deep endometriosis could significantly impair detrusor functions. Authors conducted preoperative urodynamic evaluation to assess bladder function in asymptomatic patients and found that detrusor overactivity was correlated with the presence of deep endometriosis (Serati*, et al.*, 2013).

Recommendation (100)

Routine ultrasound monitoring of asymptomatic endometriosis can be considered.	⊕◯◯◯

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 (weak 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.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question VIII.2)

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IX. Primary prevention of endometriosis

Primary prevention is aimed at protecting healthy, asymptomatic women from developing endometriosis.

Since the cause of endometriosis is unknown, the potential of primary prevention is limited. One of the risk factors for endometriosis seems to be having a first-degree family member with the disease, although the specific genetic origin of the association is still unknown. The increased disease prevalence which has been found in first-degree relatives of women with endometriosis results in questions from patients and family members on how they can prevent the development of endometriosis. Therefore, we performed a literature search for interventions that could influence the development of endometriosis, although not specifically for women with increased risk for endometriosis. However, interventions for prevention of disease development could be beneficial for these women as well.

Prevention of recurrence, or secondary prevention of endometriosis is covered in chapter IV.

PICO Question: Is there a role for primary prevention of endometriosis?

IX.1 Risk factors and prevention

Epidemiological data suggest that early menarche, shorter cycle length, long and heavy menstrual flow, lean body size and reduced gravidity/parity are associated with increased risk of developing endometriosis (Parazzini*, et al.*, 2017, Shafrir*, et al.*, 2018). Available data regarding exposure to environmental pollutants, such as dioxins and polychlorinated biphenyls, do not draw a firm conclusion about the risk of developing endometriosis later in life (Cano-Sancho*, et al.*, 2019). Nickel allergy seems to be a risk factor for endometriosis (Yuk*, et al.*, 2015).

To date there is no robust evidence supporting a significant association between diet and endometriosis, although women with endometriosis seem to consume fewer vegetables, fruits (particularly citrus fruits), dairy products, as well as foods rich of vitamin D and omega-3 polyunsaturated fatty acids and more red meat, coffee and trans fats (Harris*, et al.*, 2018, Nodler*, et al.*, 2019, Parazzini*, et al.*, 2013b).

In a review by Hansen *et al.* on endometriosis, dysmenorrhea, and diet, one large included prospective cohort study reported that increased intake of long-chain omega-3 fatty acids lowered the risk of endometriosis, while increasing trans-unsaturated fatty acid intake increased the risk of endometriosis, indicating that there may be modifiable risk factors (Hansen and Knudsen, 2013, Missmer*, et al.*, 2010).

Women with endometriosis were found to have lower vitamin D status when compared with women without endometriosis, and a negative relationship between vitamin D levels and severity of endometriosis was observed (Qiu*, et al.*, 2020). Recent data provides evidence for an association between alcohol consumption and endometriosis risk (Parazzini*, et al.*, 2013a), but not for tobacco smoking (Bravi*, et al.*, 2014). Although physical activity does not seem to reduce the risk of endometriosis, it may play a positive role in reducing endometriosis-associated pain (Ricci*, et al.*, 2016).

When comparing women with surgically diagnosed endometriosis to women without a diagnosis of endometriosis, there is evidence that current use of oral contraceptives has a protective effect against the development of endometriosis, but this effect is not observed in past or ever contraceptive users (Vercellini*, et al.*, 2011). However, the protective effect observed in current users can be related to the postponement of surgical evaluation due to temporary suppression of pain (Vercellini*, et al.*, 2011).

Recommendations (101-102)

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.	⊕⊕◯◯

The usefulness of hormonal contraceptives for the primary prevention of endometriosis is uncertain.	⊕⊕◯◯

Justification

The evidence on a healthy lifestyle and diet, with reduced alcohol intake and regular physical activity for the prevention of endometriosis is summarised 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 summarised 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.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question IX.1)

IX.2. Genetic predisposition

Although meta-analyses of genome-wide association studies identified some single nucleotide polymorphisms associated with endometriosis (Sapkota*, et al.*, 2015, Sapkota*, et al.*, 2017), to date there is no robust evidence to recommend any genetic test to assess the risk of developing the disease.

Recommendation (103)

Genetic testing in women with suspected or confirmed endometriosis should only be performed within a research setting.	RESEARCH-ONLY

Justification

With regards to genetic markers to identify high-risk population for developing endometriosis, the evidence is drawn from systematic reviews and meta-analyses of epidemiological/observational and genome-wide association (GWAS) studies. At this stage, no genetic test could be considered reliable for the diagnosis of endometriosis. As such, genetic testing for identifying a high-risk population for developing endometriosis, should be limited to a research setting.

Research recommendation (R27)

Research should further consider the genetic background of endometriosis, which may not be a monogenic disorder, and translate findings into validated tests that can be used in diagnosis and prevention.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question IX.2).

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X. Endometriosis and cancer

Endometriosis, although non-malignant, shares similar features with cancer, such as resistance to apoptosis, development of local and distant foci, invasion of other tissues, and chronic inflammatory milieu. The possible link between endometriosis and cancer is a concern for many clinicians and patients. However, the evidence on this link, and its translation into clinical practice in terms of information to patients and early detection of cancer, are unclear. In addition, recent publications suggest the presence of somatic cancer-driver mutations in endometriosis lesions that may be associated with ovarian cancer development and progression. There is concern and uncertainty also as to whether treatment for endometriosis (hormone treatment, surgery) may increase cancer risk. These questions with regards to cancer and endometriosis are discussed below.

X.1. Link between endometriosis and cancer

PICO Question: Are endometriosis patients at increased risk of cancer?

Based on a systematic review and meta-analysis of 49 cohort or case-control studies, endometriosis is associated with a very small and not statistically significant increased risk of cancer overall (summary relative risk (SRR) 1.07; 95% CI 0.98 to 1.16) (Kvaskoff*, et al.*, 2020).

Specifically, endometriosis diagnosis is associated with a higher risk of ovarian cancer (SRR 1.93), particularly the clear-cell (SRR 3.44) and endometrioid histotypes (SRR 2.33), breast cancer (SRR 1.04), and thyroid cancer (SRR 1.39) (Kvaskoff*, et al.*, 2020). The review reported no increased risk of colorectal cancer (SRR 1.00), and a lower risk of cervical cancer (SRR 0.68) in women with endometriosis. This lower risk of cervical cancer (-32%) could be attributed to higher cervical surveillance and earlier detection in women with endometriosis. The meta-analysis stresses several complex methodological issues that must be considered when interpreting findings and weighing results. Associations with endometrial cancer and cutaneous melanoma are indeed unclear as they varied in sensitivity analyses, with evidence of important impact of methodologic bias. Most of the evaluated studies (53%) were rated as having serious or critical risk of bias, with impactful heterogeneity across studies.

Associations with other cancer types either show high potential for bias (endometrial cancer, cutaneous melanoma) or have been too sparsely documented to make valid conclusions (Kvaskoff*, et al.*, 2020).

Very few studies provided estimates by endometriosis subtype. The meta-analysis shows a higher risk of ovarian cancer associated with endometrioma (SRR 5.41), although this result should be interpreted with caution given the probable methodologic bias (Kvaskoff*, et al.*, 2020). Only one study provided estimates by endometriosis subtype for the association with ovarian cancer; endometrioma and superficial peritoneal endometriosis were associated with a higher risk of clear-cell and endometroid tumours (and serous tumours for endometrioma), but deep endometriosis was not associated with ovarian cancer risk (Saavalainen*, et al.*, 2018).

Very few studies reported results by age at diagnosis or menopausal status. The association between endometriosis and ovarian cancer risk was reported to increase linearly with age at endometrioma diagnosis in one Japanese prospective cohort study (Kobayashi*, et al.*, 2007), but the relationship was less clear in a large retrospective Danish study showing stronger associations for the 30-39 and ≥50 years age categories (Mogensen*, et al.*, 2016). In the latter study, a similar association was reported between age at endometriosis diagnosis and endometrial cancer risk. The association between endometriosis and breast cancer was stronger in women aged at least 50 years at endometriosis

diagnosis in two studies (Bertelsen, *et al.*, 2007, Mogensen, *et al.*, 2016). The association between endometriosis and breast cancer did not differ according to menopausal status at breast cancer diagnosis in a prospective cohort study (Farland, *et al.*, 2016), but it was stronger in premenopausal women in two early population-based case-control studies (Moseson, *et al.*, 1993, Weiss, *et al.*, 1999). Overall, the currently available data is insufficient to make any conclusion on the association by age or menopausal status.

Recommendation (104)

Clinicians should inform women with endometriosis requesting information on their risk of developing cancer that endometriosis is not associated with a significantly higher risk of cancer overall. Although endometriosis is associated with a higher risk of ovarian, breast, and thyroid cancers in particular, the increase in absolute risk compared with women in the general population is low.	⊕⊕◯◯

Justification

The data show a higher risk of ovarian, breast, and thyroid cancer in women with endometriosis, although the increase compared to the general population is low (+0.5% to +1.2%).. As the risk of developing cancer is a major concern in some women with endometriosis; a strong recommendation for information provision was formulated. Further guidance on how information can be provided is included in the next section.

Research recommendation (R28)

Future studies should investigate the association between endometriosis and cancer using a prospective design, with a long duration of follow-up to take into account the temporality of the association, a population-based sample with standardised collection of data and recognised criteria for the definition of endometriosis, evaluate potential confounding and mediation, and, also importantly, explore heterogeneity by reporting associations according to a) endometriosis and cancer subtypes, and b) patient characteristics (age, menopausal status, etc). When exploring endometriosis macro-phenotypes, results from both exclusive and non-exclusive subtypes should be reported.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question X.1a)

NARRATIVE QUESTION: WHAT INFORMATION COULD CLINICIANS PROVIDE TO WOMEN WITH ENDOMETRIOSIS REGARDING THEIR RISK OF DEVELOPING CANCER?

Based on the currently available evidence, the increase in absolute risk for cancer in women with endometriosis is very small (Kvaskoff, *et al.*, 2020):

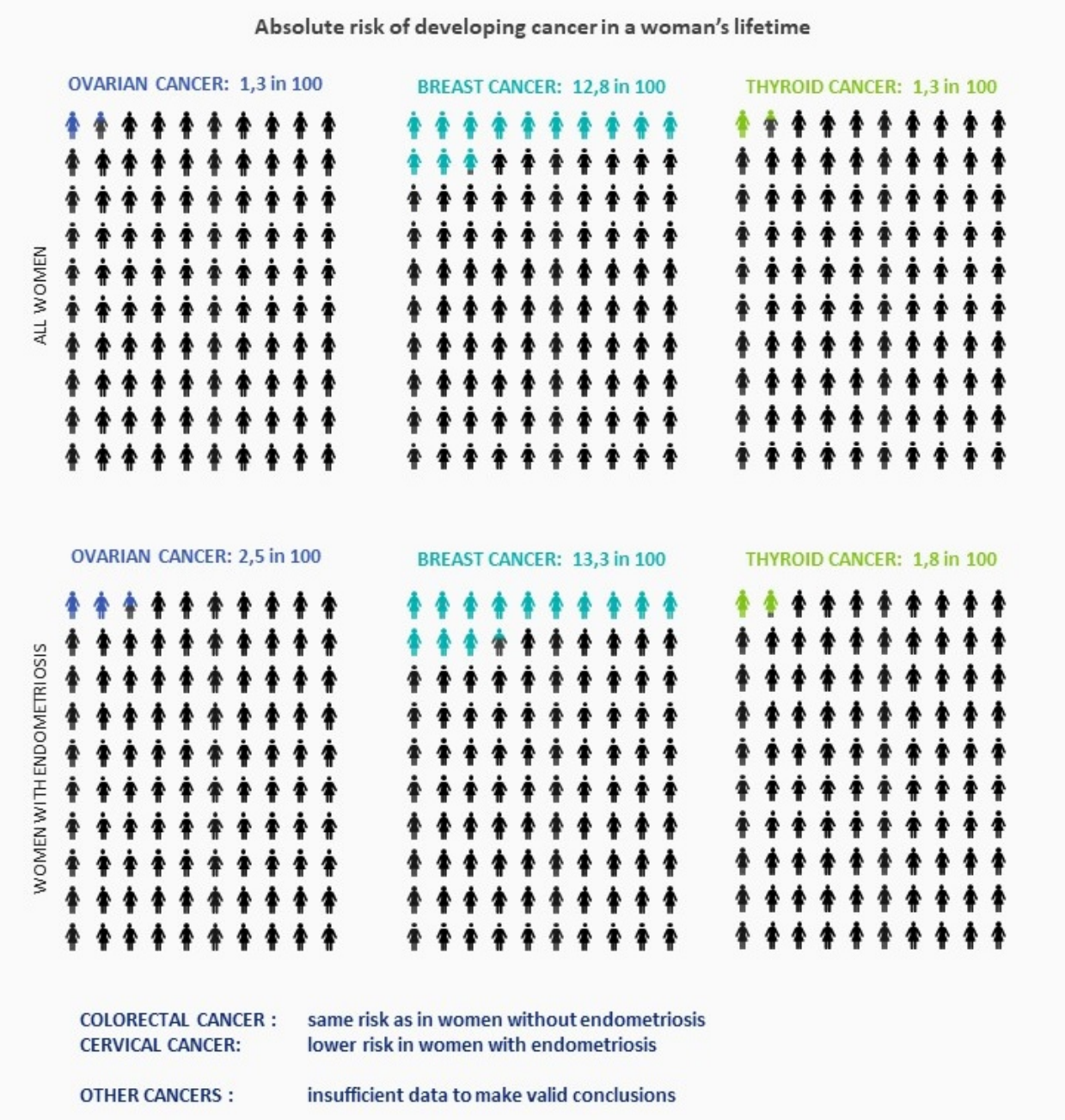
	Absolute risk of developing cancer in a woman's lifetime		Increase in risk in women with endometriosis
	All women	Women with endometriosis	
Ovarian cancer	1.3 %	2.5 %	+1.2 %
Breast cancer	12.8 %	13.3 %	+0.5 %
Thyroid cancer	1.3 %	1.8 %	+0.5 %

Although endometriosis is associated with the risk of some cancers, given the low absolute risks of ovarian, breast, and thyroid cancer in people with endometriosis relative to people without (increases of +1.2%, +0.5%, and +0.5%, respectively), and the uncertainty with regards to the risk of other cancers, endometriosis patients may be reassured that their cancer risk is low and close to that of people without the disease.

Recommendation (105)

The GDG recommends that clinicians reassure women with endometriosis with regards to their cancer risk and address their concern to reduce their risk by recommending general cancer prevention measures (avoiding smoking, maintaining a healthy weight, exercising regularly, having a balanced diet with high intakes of fruits and vegetables and low intakes of alcohol, and using sun protection).	GPP

Infographic



Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question IX.1b)

X.1.a Somatic mutations

NARRATIVE QUESTION: ARE SOMATIC MUTATIONS IN DEEP ENDOMETRIOSIS OF PATIENTS WITHOUT CANCER PREDICTIVE FOR OVARIAN CANCER DEVELOPMENT AND/OR PROGRESSION?

Endometrioma has been posited as a direct precursor for clear-cell and endometrioid ovarian cancer (Anglesio and Yong, 2017). However, epidemiologic, histologic, genetic, and biochemical data have been conflicting (Bulun, *et al.*, 2019, Guo, 2020, Kvaskoff, *et al.*, 2020, Vigano, *et al.*, 2006). Some authors described atypical endometriosis in a spatial and chronological association with ovarian cancer (Van Gorp, *et al.*, 2004). Although a direct progression has been only rarely demonstrated, emerging evidence suggests genetic associations between endometriosis and ovarian cancer. Several genetic studies have shown that endometriotic lesions have mutations or alterations in genes directly related to neoplasms, particularly *PTEN*, *TP53*, *KRAS*, and *ARID1A* (Akahane, *et al.*, 2007, Amemiya, *et al.*, 2004, Borrelli, *et al.*, 2016, Er, *et al.*, 2016, Siufi Neto, *et al.*, 2014).

Nevertheless, more recently, the presence of cancer-driver mutations was investigated in various tissues of patients without cancer (Bulun, *et al.*, 2019, Yong, *et al.*, 2021). Aside from endometrioma (Anglesio, *et al.*, 2015, Suda, *et al.*, 2018), somatic mutations in cancer-associated genes were observed in a quarter to a third of patients with deep endometriosis – a subtype that rarely undergoes malignant transformation (Anglesio, *et al.*, 2017, Lac, *et al.*, 2019b); in about 28% of patients with incisional endometriosis (an iatrogenic form of endometriosis occurring in the resulting surgical scars of obstetric/ gynaecological procedures) (Lac, *et al.*, 2019b); and in over 50% of normal endometrium samples (Lac, *et al.*, 2019a).

Conclusion

Based on the limited literature and controversial findings, there is little evidence that somatic mutations in patients with deep endometriosis may be predictive of development and/or progression of ovarian cancer

Research recommendation (R29)

More research needs to be performed on the mutational and epigenetic profile of endometriosis tissue, endometrium from endometriosis patients and normal endometrium from women of different ages and reproductive histories. Among women with endometriosis, exclusive macro-phenotypes of endometriosis should be investigated.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question X.1c).

X.1.b Impact of hormone treatments

PICO QUESTION: DOES THE USE OF HORMONE TREATMENTS INCREASE THE RISK OF CANCER?

Hormone treatments (OCP, progestogens) are recommended for the treatment of endometriosis-associated pain and are widely used (See chapter II medical treatment for pain). As symptoms often reappear after discontinuation, the treatments are often used long-term, which may pose patients at risk of safety issues (Ferrero, *et al.*, 2015, Ferrero, *et al.*, 2018).

The neoplastic effects of the oral contraceptive pill (OCP) have been extensively studied. A review on the safety of medical treatments for endometriosis suggested an inverse association between duration of OCP use and ovarian cancer risk (for women using oral contraception for 4 and 8 years, the RR was 0.60 and 0.49, respectively) and endometrial cancer risk (for women using oral contraception for 4 and 8 years, the RR was 0.46 and 0.34, respectively); whereas the use of OCP was associated with an increased risk of breast cancer (RR between 1.09 and 1.38) and cervical cancer (RR between 1.1 and 2.2) (Berlanda*, et al.*, 2016).

In the general population, OCP users have a 20% to 30% lower risk of ovarian cancer than never-users (Havrilesky*, et al.*, 2013, Wentzensen*, et al.*, 2016) . Furthermore, this risk reduction has been shown to be strengthened with the length of oral contraceptive use; long-term OCP use (10 years or more) was associated with a 40% lower ovarian cancer risk (HR 0.60; 95% CI 0.47 to 0.76) compared with OCP use for less than 1 year in the NIH-AARP Diet and Health Study, a large prospective population-based cohort (Michels*, et al.*, 2018). This lower risk with longer durations of OCP use was observed for all histotypes of ovarian cancer except for mucinous tumours (Wentzensen*, et al.*, 2016) and across several lifestyle characteristics (smoking, BMI, physical activity) (Michels*, et al.*, 2018).

In the NIH-AARP Diet and Health Study, women who have ever used OCPs had a 34% lower risk of endometrial cancer than women who have never used oral contraceptives and this risk decrease was more pronounced with long durations of use (HR 0.66; 95%CI 0.56 to 0.78 for ≥10 years vs. 1 year or less) (Michels*, et al.*, 2018). The strongest risk reductions were observed in those long-term users of oral contraceptives who were current smokers, obese, or exercised moderately or infrequently. In an Italian case-control study, OCP use was associated with 36% lower odds of endometrial cancer (95% CI 0.43-0.96) (Zucchetto*, et al.*, 2009).

In 2017, a large nationwide, registry-based prospective Danish study reported breast cancer risks associated with OCP use, based on 1.8 million women and over 11,000 breast cancer cases (Morch*, et al.*, 2018). Compared with women who had never used hormonal contraception, the relative risk of breast cancer among all current and recent users of OCP was 1.20 (95% CI 1.14 to 1.26). This risk increased from 1.09 (95% CI 0.96 to 1.23) with less than 1 year of use to 1.38 (95% CI 1.26 to 1.51) with more than 10 years of use. In the NIH-AARP Diet and Health Study, there was no association between duration of OCP use and breast cancer risk (P for trend=0.23) (Michels*, et al.*, 2018): .

A systematic review of 28 studies showed that compared with never users of OCPs, the relative risk of cervical cancer increased with increasing duration of use: for durations of approximately less than 5 years, 5-9 years, and 10 or more years, respectively, the summary relative risks were 1.1 (95% CI 1.1 to 1.2), 1.6 (95% CI 1.4 to 1.7), and 2.2 (95% CI 1.9 to 2.4) for all women (Smith*, et al.*, 2003).

A meta-analysis showed that women who have ever used OCPs had a 14% lower risk of colorectal cancer than women who have never used OCPs (Gierisch*, et al.*, 2013), although there was no association between duration of OCP use and colorectal cancer risk in the NIH-AARP Diet and Health Study (Michels*, et al.*, 2018). No association was observed between OCP use and pancreatic cancer (Butt*, et al.*) or thyroid cancer (Braganza*, et al.*, 2014) in two large prospective studies.

Scanty evidence is available on the neoplastic effect of progestins and their long-term use. However, an association between use of progestins for contraception and an increased risk of breast cancer has not been reported (Berlanda*, et al.*, 2016). Finally, a Swedish nationwide, registry-based nested case-control study including 220 ovarian cancer cases and 416 controls, all among women with endometriosis, reported no appreciable impact of hormone treatments (OCP, progestogen, danazol, GnRH agonists, or menopausal hormone therapy) on ovarian cancer risk among women with endometriosis (Melin*, et al.*, 2013).

Recommendation (106)

Clinicians should reassure women with endometriosis about the risk of malignancy associated with the use of hormonal contraceptives.	⊕○○○

Justification

Robust evidence from studies in the general population shows that the risks of ovarian, endometrial, and colorectal cancers are decreased in women who use OCPs, whereas the risks of breast and cervical cancers are increased. . However, the higher risk of cervical cancer related to OCP use may be counterbalanced by the lower cervical cancer risk related to endometriosis, and the risk reduction for ovarian, endometrial, and colorectal cancers may outweigh the increased risk for breast cancer. The risk reductions and risk increases are more pronounced for longer durations of use of the OCP.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question X.1d).

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X.2. Monitoring for detection of malignancy

PICO Question: Should women with endometriosis be monitored for detection of malignancy?

Based on the increase in lifetime risks of ovarian, breast, and thyroid cancer in endometriosis patients, monitoring could be advocated. However, the data discussed above show that the increased risk is very small compared with women in the general population (0.5-1.2%) (Kvaskoff*, et al.*, 2020).

Monitoring for ovarian malignancy could be performed by CA-125 measurement, or imaging, although the value is unclear, even in women without endometriosis. Randomised-controlled trials have shown no benefit of serum CA-125 measurements or transvaginal ultrasound on early detection of ovarian cancer or mortality reduction (Buys*, et al.*, 2011, Jacobs*, et al.*, 2016). In fact, significant harm has been reported for those receiving false-positive test results for ovarian cancer (unnecessary surgery, surgical complications, infections, or cardiovascular/pulmonary complications) (Buys*, et al.*, 2011).

Still, monitoring, by regular CA-125 measurements or ultrasound scans, is performed in women with high risk of developing ovarian cancer, such as those with family history of ovarian/breast cancer or a known germline mutation These women may have a lifetime risk of ovarian cancer of up to 50% compared to the 1.3% risk in the general population (and 2.5% in women with endometriosis). In some of these high-risk women, prophylactic bilateral salpingo-oophorectomy (BSO) is recommended for further reduction of ovarian cancer risk (Berek*, et al.*, 2010); however, BSO is associated with important health risks of starkly higher incidence than the risk of ovarian cancer. In premenopausal women, BSO can result in cardiovascular disease, depression, arthritis, asthma, chronic obstructive pulmonary disease, and osteoporosis. In post-menopausal women, BSO has been linked to cardiovascular diseases, anxiety, sexual function disorders, fracture, neurologic disorders, and cognitive impairment (Kvaskoff*, et al.*, 2020, Parker*, et al.*, 2009). Considering the lifetime risk of ovarian cancer and the significant harm, BSO is not recommended in women with endometriosis without further risk factors for ovarian cancer.

Monitoring for other types of malignancy is not justified given the low absolute breast and thyroid cancer risk in women with endometriosis.

An area of uncertainty is monitoring for malignancy among asymptomatic patients and postmenopausal women with endometrioma.

Recommendations (107-108)

In women with endometriosis, clinicians should not systematically perform cancer screening beyond the existing population-based cancer screening guidelines.	⊕⊕◯◯

Clinicians can consider cancer screening according to local guidelines in individual patients that have additional risk factors, e.g., strong family history, specific germline mutations.	GPP

Justification

Given the small increases in the lifetime risk of ovarian cancer in endometriosis patients, regular screening through serum CA-125 measurements or trans-vaginal ultrasound has no benefit on early detection or mortality reduction for ovarian cancer. Conversely, significant harm has been reported for women receiving false-positive test results. In the absence of significant risk factors, bilateral salpingo-oophorectomy outweighs the risk of ovarian cancer.

Research recommendation (R30)

More data are needed on the malignant transformation of endometrioma and endometriosis in general to guide the need for monitoring.

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question X.2)

References

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X.3. Surgery and malignancy

PICO Question: Does surgery for endometriosis change the future risk of cancer?

Some authors have advocated "earlier and more meticulous surgical intervention for complete disease removal" to reduce future ovarian cancer risk (Nezhat, *et al.*, 2008). Others have challenged this position on the basis that preventative surgery may be extended to asymptomatic women and argued that given the relapsing nature of endometriosis, it is unlikely that preventative surgery would reduce the future risk substantially (Vercellini, *et al.*, 2009).

A nationwide, registry-based study of all women with a first-time discharge diagnosis of endometriosis (70%-80% with endometrioma regardless of other types) in 1969-2007 in Sweden identified 183 cases of epithelial ovarian cancer in women with endometriosis and compared them with 318 matched controls with endometriosis and no ovarian cancer using a nested case-control design (Melin, *et al.*, 2013). Those who had undergone unilateral oophorectomy or extirpation of all visible endometriosis at surgery for endometriosis had a dramatically reduced risk of ovarian cancer in later life. This risk reduction was more pronounced in those who had unilateral oophorectomy (OR 0.10; 95%CI 0.03 to 0.36) compared with those who had excision without removing the affected ovary (OR 0.29; 95%CI 0.10 to 0.84). Other types of surgical treatment (tubal ligation, unilateral or bilateral salpingectomy, hysterectomy) were not significantly associated with the risk of epithelial ovarian cancer.

A population-based case-control study of 812 women with ovarian cancer and 1313 controls explored the relationship between pre-existing benign ovarian conditions and risk of ovarian cancer, as well as the reduction in such risk associated with ovarian surgery following the diagnosis of the benign condition (Rossing, *et al.*, 2008). However, the study lacked statistical power (only 175 participants reported endometriosis) and produced imprecise estimates, with wide CIs that often overlapped across subgroups. The association between self-reported endometriosis and ovarian cancer did not significantly differ between women who reported ovarian surgery after their endometriosis (unilateral oophorectomy, excision of a cyst or of a partial ovary; OR 1.4; 95%CI 1.0 to 2.0) and those who did not (OR 1.0; 95%CI 0.5 to 2.2). The OR for the association between self-reported endometriosis and ovarian cancer was 0.8 (95%CI 0.3 to 2.1) in women who reported unilateral oophorectomy, whereas it was 3.3 (95%CI 0.7 to 15.3) in those who reported a lesser extent of ovarian surgery (cystectomy or partial oophorectomy). Self-reported endometriosis was associated with a three-fold increase in the risk of endometrioid and clear-cell invasive tumours (OR 3.2; 95%CI 1.9 to 5.6), with a smaller OR in those who underwent ovarian surgery (OR 1.6; 95%CI 0.4 to 5.7).

In a retrospective cross-sectional study of 485 women who had excision of endometrioma, 4 (0.8%) developed ovarian cancer (Haraguchi, *et al.*, 2016). These all occurred in women with recurrence of their endometrioma. Age at endometrioma excision ranged from 32 to 41.

Recommendation (109)

Clinicians should be aware that there is epidemiological data, mostly on ovarian endometriosis, showing that complete excision of visible endometriosis may reduce the risk of ovarian cancer. The potential benefits should be weighed against the risks of surgery (morbidity, pain, and ovarian reserve).	⊕⊕◯◯

Justification

Surgical excision of endometriosis, from the ovaries and from other locations, may reduce the risk of subsequent ovarian cancer. However, removal of the affected ovary, where appropriate, may have a

bigger cancer risk reduction effect than excision of disease and preservation of the ovary. If endometriosis involves both ovaries, BSO should be considered with caution with regards to other long-term health risks, as detailed in section X.2

Further information

Details of the literature study and evidence tables are available in Annex 7 and Annex 8 (question X.3)

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Annex 1: Guideline group

This guideline was developed by the ESHRE Endometriosis Guideline Development Group (GDG) 2022.

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Treatment of endometriosis-associated pain – Non-Pharmacological

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Josepha Goetz-Collinet	

Treatment of endometriosis-associated infertility

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Munawar Hussain	Southend University Hospital, UK
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Carla Tomassetti	University Hospitals Leuven, Dept. Obstetrics and Gynaecology, Leuven University Fertility Center, Belgium; KU Leuven, Faculty of Medicine, Dept. Development and Regeneration, LEERM (Lab of Endometrium, Endometriosis and Reproductive Medicine), Leuven, Belgium
Alexandra Bianco-Anil	EndoFrance, French patients' Association, France
Josepha Goetz-Collinet	

Endometriosis in adolescence

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Gürkan Uncu	Uludag University, Bursa, Turkey
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Menopause in women with endometriosis

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Christian Becker	Endometriosis CaRe Centre Oxford, Nuffield Department of Women's and Reproductive Health, University of Oxford, UK
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Asymptomatic + Extrapelvic Endometriosis

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Réka Brubel	Semmelweis University, Faculty of Medicine, Budapest, Hungary
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Helen McLaughlin	Endometriosis advocate, London; Endometriosis UK

Declarations of interest

All members of the guideline development group were asked to declare possible conflicts of interest by means of the disclosure forms (see *ESHRE Manual for Guideline Development*).

	Conflicts of Interest
Christian Becker	Grants from Bayer Healthcare and the European Commission; Participation on a Data Safety Monitoring Board or Advisory Board with ObsEva (Data Safety Monitoring Group) and Myovant (Scientific Advisory Group).
Attila Bokor	Grants from FEMaLE executive board member and European Comission Horizon 2020 grant; consulting fees from Ethicon Endo Surgery, Medtronic; honoraria for lectures from Ethicon; and support for meeting attendance from Gedeon Richter
Andrew Horne	Grants from MRC, NIHR, CSO, Roche Diagnostics, Astra Zeneca, Ferring; Consulting fees from Roche Diagnostics, Nordic Pharma, Chugai and Benevolent Al Bio Limited all paid to the institution; a pending patent on Serum endometriosis biomarker; he is also Chair of TSC for STOP-OHSS and CERM trials
Oskari Heikinheimo	Consulting fees, speaker's fees from Gedeon Richter and Bayer AG; advisory board member for Gedeon Richter and Bayer AG.
Ludwig Kiesel	Consulting fees from Gedeon Richter, AstraZeneca, Novartis, Dr. KADE/Besins, Palleos Healthcare, Roche, Mithra; honoraria for lectures from Gedeon Richter, AstraZeneca, Novartis, Dr. KADE/Besins, Palleos Healthcare, Roche, Mithra; support for attending meetings from Gedeon Richter, AstraZeneca, Novartis, Dr. KADE/Besins, Palleos Healthcare, Roche, Mithra; he also has a leadership role in the German Society of Gynecological Endocrinology (DGGEF)
Marina Kvaskoff	Grants from French Foundation for Medical Research (FRM), Australian Ministry of Health, Medical Research Future Fund, and French National Cancer Institute; support for meeting attendance from European Society for Gynaecological Endoscopy (ESGE), European Congress on Endometriosis (EEC) and ESHRE; She is an advisory Board Member, FEMaLe Project (Finding Endometriosis Using Machine Learning), Scientific Committee Chair for the French Foundation for Research on Endometriosis and Scientific Committee Chair for the ComPaRe-Endometriosis cohort.
Annemiek Nap	Grants from Merck SA and Ferring; speaker fees from Merck SA and Ferring; support for meeting attendance from Merck SA; Participation on a Data Safety Monitoring Board or Advisory Board with Nordic Pharma and Merck SA; she also is a board member of medical advisory board, Endometriosis Society, the Netherlands (patients advocacy group) and an executive board member World Endometriosis Society.
Katrine Petersen	None declared
Ertan Saridogan	Grants from National Institute for Health Research UK, Rosetrees Trust, Barts and the London Charity; Royalties from De Gruyter (book editor); consulting fees from Hologic; speakers fees from Hologic, Johnson & Johnson, Medtronic, Intuitive, Olympus and Karl Storz; Participation in the Medicines for Women's Health Expert Advisory Group with Medicines and Healthcare Products

	Regulatory Agency (MHRA); he is also Ambassador for the World Endometriosis Society.
Carla Tomassetti	Grants from Merck SA; Consulting fees from Gedeon Richter, Nordic Pharma and Merck SA; speaker fees from Merck SA, all paid to the institution; and support for meeting attendance from Ferring, Gedeon Richter, Merck SA.
Nehalennia van Hanegem	None declared
Nicolas Vulliemoz	Support for meeting attendance from Merck SA
Femke Jansen	None declared
Kathleen King	None declared
Nathalie Vermeulen	None declared

Annex 2: Abbreviations

3-D	3 dimensional
AFC	Antral follicle count
AMH	Anti-Müllerian hormone
ART	Assisted reproduction technologies
AUC	Area under the curve
BDI	Beck Depression Inventory
BMD	bone mineral density
BSO	bilateral salpingo-oophorectomy
CA-125	cancer antigen 125
CAM	complementary and alternative medicine
CEE	conjugated equine estrogens
CGRP	calcitonin gene-related peptide
CT	computed tomography
EE	ethinylestradiol
EHP30	Endometriosis Health Profile instrument (30 questions)
ENG	etonogestrel-releasing subdermal implant
EQ-5D	Instrument to describe and value health
FSH	Follicle stimulating hormone
GDG	Guideline development group
GnRH	gonadotrophin releasing hormone
HIFU	high-intensity focussed ultrasound
HMG	human menopausal gonadotropin
HRT	hormone replacement treatment
Hx	Hysterectomy
IPI	Intraperitoneal insemination
IUI	intrauterine insemination
LH	Luteinizing hormone
LNG-IUS	levonorgestrel intrauterine system
LP	long OS protocol
LUNA	laparoscopic uterosacral nerve ablation
MAR	Medically assisted reproduction
MCS	Mental Component Score
MD	mean difference
MHT	menopausal hormone therapy
MRI	magnetic resonance imaging
MRS	Menopause Rating Scale
NA	norethindrone acetate
NPY	neuropeptide Y
NSAIDs	non-steroidal anti-inflammatory drugs
OCP	oral contraceptive pill
OR	Odds ratio
ORC	oxidised regenerated cellulose
OS	ovarian stimulation
PCS	Physical Component Score

PET-CT	Positron emission tomography–computed tomography
PGP 9.5	protein gene product 9.5
PR	pregnancy rate
PRO	patient-reported outcome
PSN	presacral neurectomy
QoL	quality of life
QoSL	quality of sexual life
rASRM	Revised American Society for Reproductive Medicine score
RR	Relative risk
SF-12	self-reported outcome measure instrument (short form)
SF-36	self-reported outcome measure instrument (long form)
SOF	Summary of Findings
SP	substance P
SPE	superficial peritoneal endometriosis
TAS	transabdominal ultrasonography
TENS	Transcutaneous Electrical Nerve Stimulation
TVUS	transvaginal ultrasound
ULP	ultralong OS protocol
VAS	Visual analogue scale
VATS	Video-assisted thoracoscopy
VIP	vasoactive intestinal polypeptide

Annex 3: Key Questions

Diagnosis of endometriosis

Question I.1 Can clinical symptoms predict the presence of endometriosis?

Question I.2 Does the use of symptom diaries or questionnaires compared to traditional history taking lead to improved or earlier diagnosis of endometriosis?

Question I.3 Does clinical examination of symptomatic women reliably predict the presence of endometriosis?

Question I.4 are medical technologies reliable in diagnosing endometriosis and establishing the extent of the disease?

Question I.5 Does diagnostic laparoscopy compared to empirical medical treatment result in better symptom management in women suspected of endometriosis?

Question I.6 Is long term monitoring of women with endometriosis beneficial in preventing adverse outcomes (recurrence, complications, malignancy)?

Question I.7 Does early diagnosis of endometriosis versus late diagnosis lead to better quality of life?

Treatment of endometriosis-associated pain

Question II.1 Are analgesics effective for symptomatic relief of painful symptoms associated with endometriosis?

Question II.2 Are hormone therapies effective for painful symptoms associated with endometriosis?

Question II.3 Is surgery effective for treatment of pain associated with endometriosis?

Question II.3b Is there a subgroup of women with confirmed endometriosis who respond better to surgery than others?

Question II.4 Are medical therapies effective as an adjunct to surgical therapy?

Question II.5 Are surgical therapies more effective than medical therapies for women with endometriosis with pain symptoms?

Question II.6 What non-medical management strategies are effective for symptoms associated with endometriosis (pain and Quality of Life)?

Treatment of endometriosis-associated infertility

Question III.1 Are hormone/medical therapies effective for treatment of endometriosis-associated infertility?

Question III.2 In women with endometriosis, is surgery effective to increase the chance of natural pregnancy?

Question III.3 Which patients need treatment with assisted reproduction technology after surgery?

Question III.4 Is medically assisted reproduction effective for infertility associated with endometriosis?

Question III.5 Are medical therapies effective as an adjunct to MAR for endometriosis-associated infertility?

Question III.6 Are surgical therapies effective as an adjunct prior to MAR for endometriosis-associated infertility?

Question III.7 What non-medical management strategies are effective for infertility associated with endometriosis ?

Question III.8 Is endometriosis an indication for fertility preservation (ovarian tissue/oocytes)?

Question III.9 What is the impact of endometriosis on pregnancy and obstetric outcomes?

Endometriosis recurrence

Question IV.1 Is there a role for secondary prevention of recurrence of disease and painful symptoms in patients treated for endometriosis?

Question IV.2 How should patients with reoccurring endometriosis or recurring symptoms be managed? Is repetitive surgery effective for symptoms associated with endometriosis?

Endometriosis and adolescence

Question V.1 Which diagnostic procedures should be applied in adolescents with possible endometriosis?

Question V.1b Should diagnosis of endometriosis in adolescents be confirmed by histology?

Question V.2 What is the best treatment for adolescents with (suspected) endometriosis?

Question V.3 Is endometriosis in adolescents an indication for fertility preservation (ovarian tissue / oocytes)?

Endometriosis and menopause

Question VI.1 Is endometriosis still active during menopause and if so, how should the symptoms be treated?

Question VI.2 Is surgical/medical treatment effective and safe in women with a history of endometriosis?

Question VI.3 Is hormone treatment effective and safe for relief of menopausal symptoms in women with a history of endometriosis?

Question VI.4 Are women with endometriosis at higher risk of experiencing menopause-related major health concerns?

Extrapelvic endometriosis

Question VII.1 How reliable is imaging for diagnosing extrapelvic endometriosis?

Question VII.2 Does treatment for extrapelvic endometriosis relieve symptoms ?

Asymptomatic Endometriosis

Question VIII.1 Is treatment beneficial for incidental finding of asymptomatic endometriosis?

Question VIII.2 Is long term monitoring of women with asymptomatic endometriosis beneficial in preventing adverse outcomes?

Primary prevention of endometriosis

Question IX.1 Is there a role for primary prevention of endometriosis?

Endometriosis and cancer

Question X.1a Are endometriosis patients at increased risk of cancer?

Question X.1b What information could clinicians provide to women with endometriosis regarding their risk of developing cancer?

Question X.1c Are somatic mutations in deep endometriosis of patients without cancer predictive for ovarian cancer development and/or progression?

Question X1.d Does the use of hormone treatments increase the risk of cancer?

Question X.2 Should women with endometriosis be monitored for detection of malignancy?

Question X.3 Does surgery for endometriosis change the future risk of cancer?

Annex 4: Methodology

Guideline development

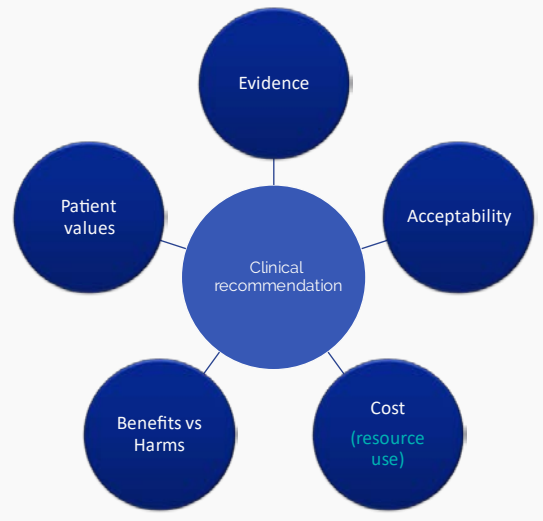
European Society of Human Reproduction and Embryology (ESHRE) guidelines are developed based on the Manual for ESHRE guideline development (N. Vermeulen, A. D'Angelo, P. de Sutter, W.L.D.M. Nelen, Manual for ESHRE guideline development, version 2017), which can be consulted at the ESHRE website (www.eshre.eu/guidelines). The principal aim of this manual is to provide stepwise advice on ESHRE guideline development for members of ESHRE guideline development groups. The manual describes a 12-step procedure for writing clinical management guidelines by the guideline development group, supported by the ESHRE methodological expert.

The current guideline was developed with support of ESHRE, which covered expenses associated with the guideline meetings (travel, hotel, and catering expenses) associated with the literature searches (library costs, costs associated with the retrieval of papers) and with the implementation of the guideline (printing, publication costs). Except for reimbursement of their travel expenses, GDG members did not receive any payment for their participation in the guideline development process.

After approval of the guideline application by the ESHRE Executive Committee, the scope of the guideline and the members of the guideline group were discussed. In composing a guideline group, we strived towards a balance in expertise, gender, and location within Europe. …

A meeting of the guideline development group was organised to discuss the key questions and redefine them through the PICO process (patients – interventions – comparison – outcome). This resulted in a final list of 42 key questions, of which 7 were answered as narrative questions, and 35 as PICO questions. Based on the defined key words, literature searches were performed by the methodological expert (N. Vermeulen). Key words were sorted to importance and used for searches in PUBMED/MEDLINE and the Cochrane library. We searched the databases from inception up to 1 december 2020.

Literature searches were performed as an iterative process. In a first step, systematic reviews and meta-analyses were collected. If no results were found, the search was extended to randomised controlled trials, and further to cohort studies and case reports, following the hierarchy of the levels of evidence. References were selected or excluded by the methodological expert and expert GDG member based on title and abstract and knowledge of the existing literature. If necessary, additional searches were performed to get the final list of papers. The quality of the selected papers was assessed by means of the quality assessment checklist, defined in the ESHRE guideline manual. Next, the evidence was collected and summarised in an evidence table. The quality assessment and completion of evidence tables were performed by the expert GDG members.



Summary of findings tables are usually prepared according to the GRADE approach for all interventions with at least two studies (RCTs) per outcome. For the interventions in the current guideline, such evidence is not available, and hence no summary of findings tables were produced.

GDG meetings were organised to discuss the draft recommendations and the supporting evidence and to reach consensus on the final formulation of the recommendations.

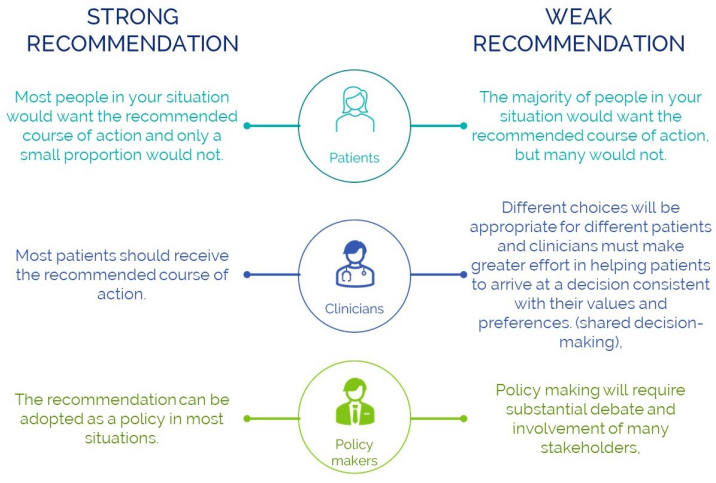
For each recommendation, it is mentioned whether it is strong or weak and what the quality of the supporting evidence was.

In the justification section, more data are provided on the interpretation of the supporting evidence and how other factors (i.e., balance between desirable and undesirable effects, certainty of the evidence of effects, certainty in how people value the outcome, and acceptability) were considered. Costs and resource impact were only discussed where relevant.

In a final step, all evidence and recommendations were combined in the ESHRE guideline: "Endometriosis"

Implications of recommendations

We labelled the recommendations as either ''strong'' or ''weak" according to the GRADE approach, with appropriate wording for each option. Suggested interpretation of strong and weak recommendations by patients, clinicians and health care policy makers is as follows:



Good practice points or GPPs are mainly based on the expertise and opinion of guideline group members. GPPs can be used to emphasize the importance of patient participation in decision making about specific procedure, provide advice on the management of specific surgical procedures for which there is an evidence-based recommendation, or advise caution where there is perceived risk of harm but no available direct evidence of such harms.

Strategy for review of the Guideline draft

After finalisation of the guideline draft, the review process was initiated. The draft guideline was published on the ESHRE website, accompanied by the reviewers' comments form and a short explanation of the review process. The guideline was open for review between 24 June and 15 August 2021.

To notify interested clinicians, we sent out an invitation to review the guideline by email to all members of the ESHRE SIG Endometriosis and Endometrial Disorders. Selected reviewers were personally invited by email. These reviewers included:

- Coordinators and deputies of the ESHRE SIGs Endometriosis and Endometrial Disorders
- The members of the endometriosis guideline group 2013
- Experts that participated in the stakeholder review in 2013
- Contact persons of international and national societies.

All reviewers that submitted comments are listed in Annex 6. The Review report, including further information on the review and a list of all comments per reviewer with the response formulated by the GDG is published on the ESHRE website.

Guideline Implementation strategy

The standard dissemination procedure for all ESHRE guidelines comprises publishing and announcement.

Each guideline is published on the ESHRE Website and in Human Reproduction. The announcement procedure includes a newsflash on the ESHRE website homepage. All participants in the annual ESHRE meeting and all related national societies and patient organisations are informed about the guideline release. The latter are asked to encourage local implementation by, for instance, translations or condensed versions, but they are also offered a website link to the original document.

Patient versions of the guideline will be developed by a subgroup of the GDG together with patient the representatives. The patient version is a translation of the recommendations in everyday language, with emphasis on questions important to patients. It aims to help patients understand the guideline's recommendations and facilitates clinical decision-making.

To further enhance implementation of the guideline, the members of the GDG, as experts in the field, will be asked to make suggestions for tailor-made implementation interventions (e.g., option grids, flow-charts, additional recommendations, addition of graphic/visual material to the guideline).

Schedule for updating the guideline.

The current guideline will be considered for revision in 2025 (four years after publication). An intermediate search for new evidence will be performed two years after publication, which will inform the GDG of the necessity of an update.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found at www.eshre.eu/guidelines.

For more details on the methodology of ESHRE guidelines, visit www.eshre.eu/guidelines

Annex 5 : Flowcharts

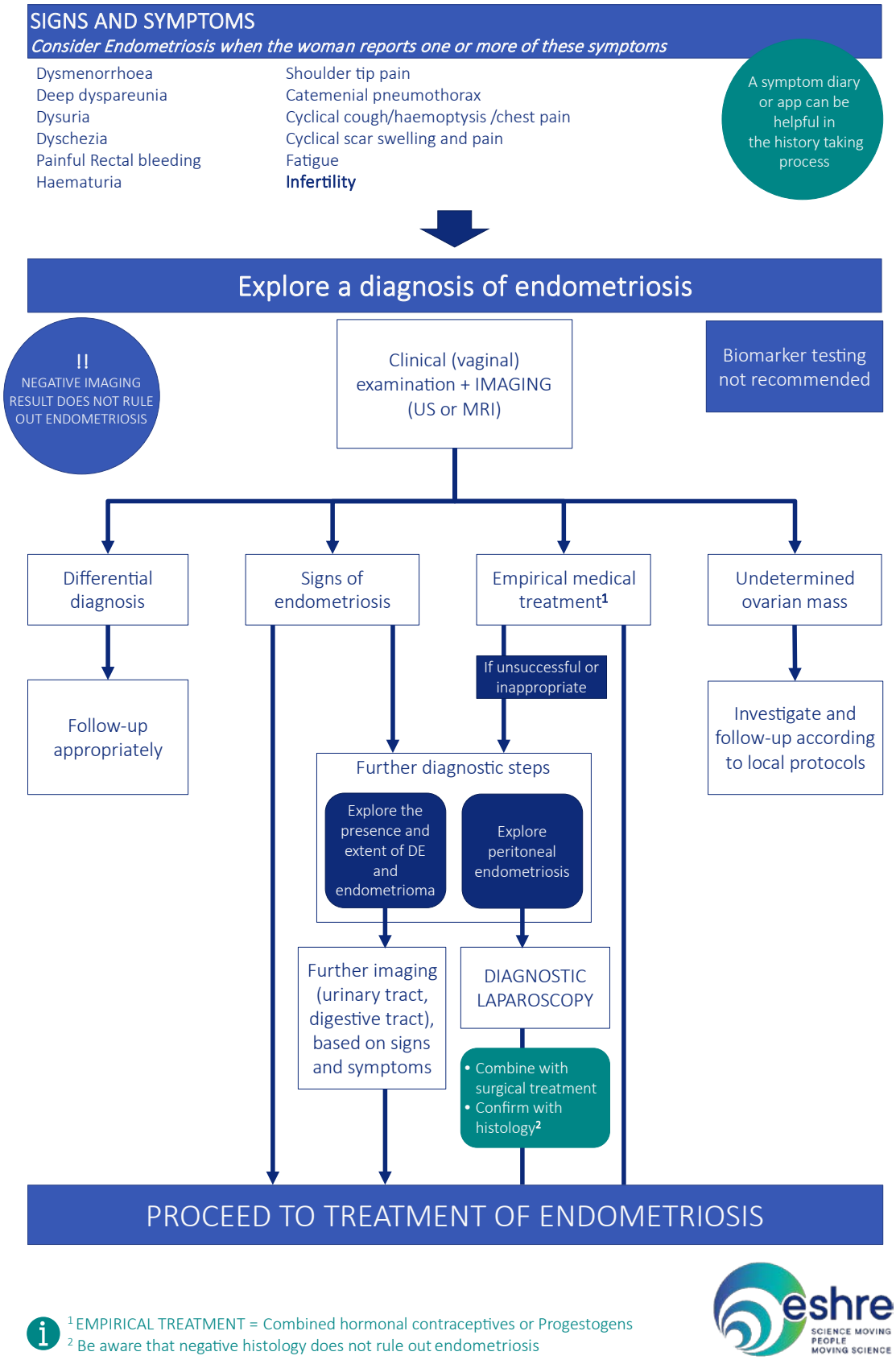
Diagnosis of endometriosis

Treatment of endometriosis - pain

Treatment of endometriosis - infertility

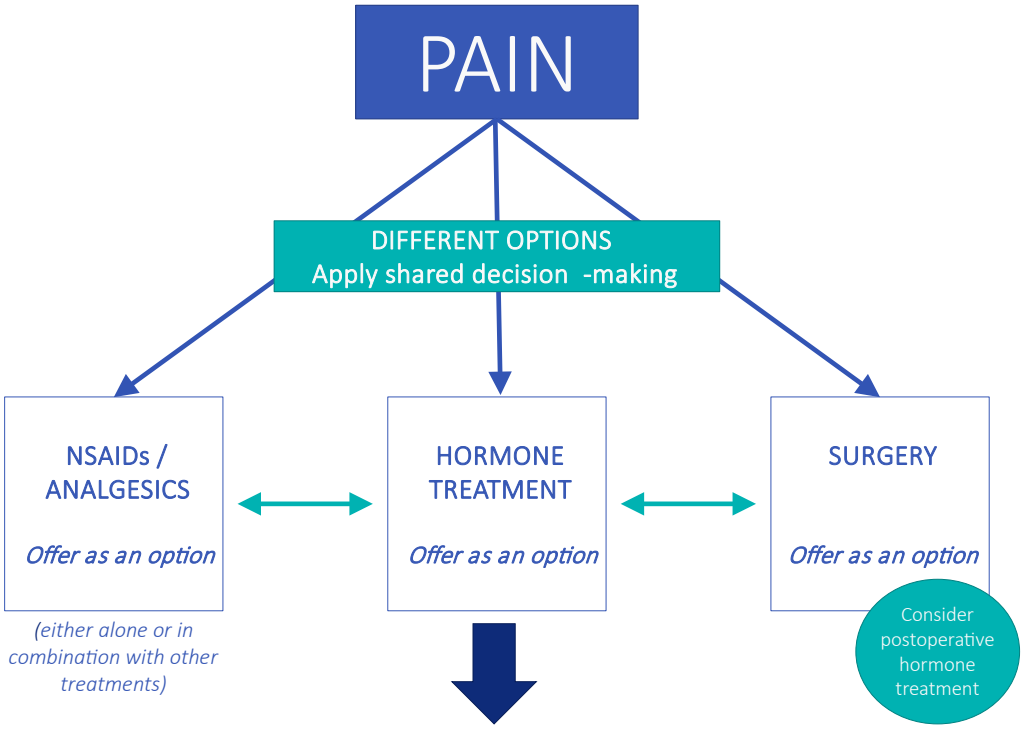
Endometriosis and pregnancy

DIAGNOSIS OF ENDOMETRIOSIS



[1] EMPIRICAL TREATMENT = Combined hormonal contraceptives or Progestogens
[2] Be aware that negative histology does not rule out endometriosis

TREATMENTS FOR ENDOMETRIOSIS

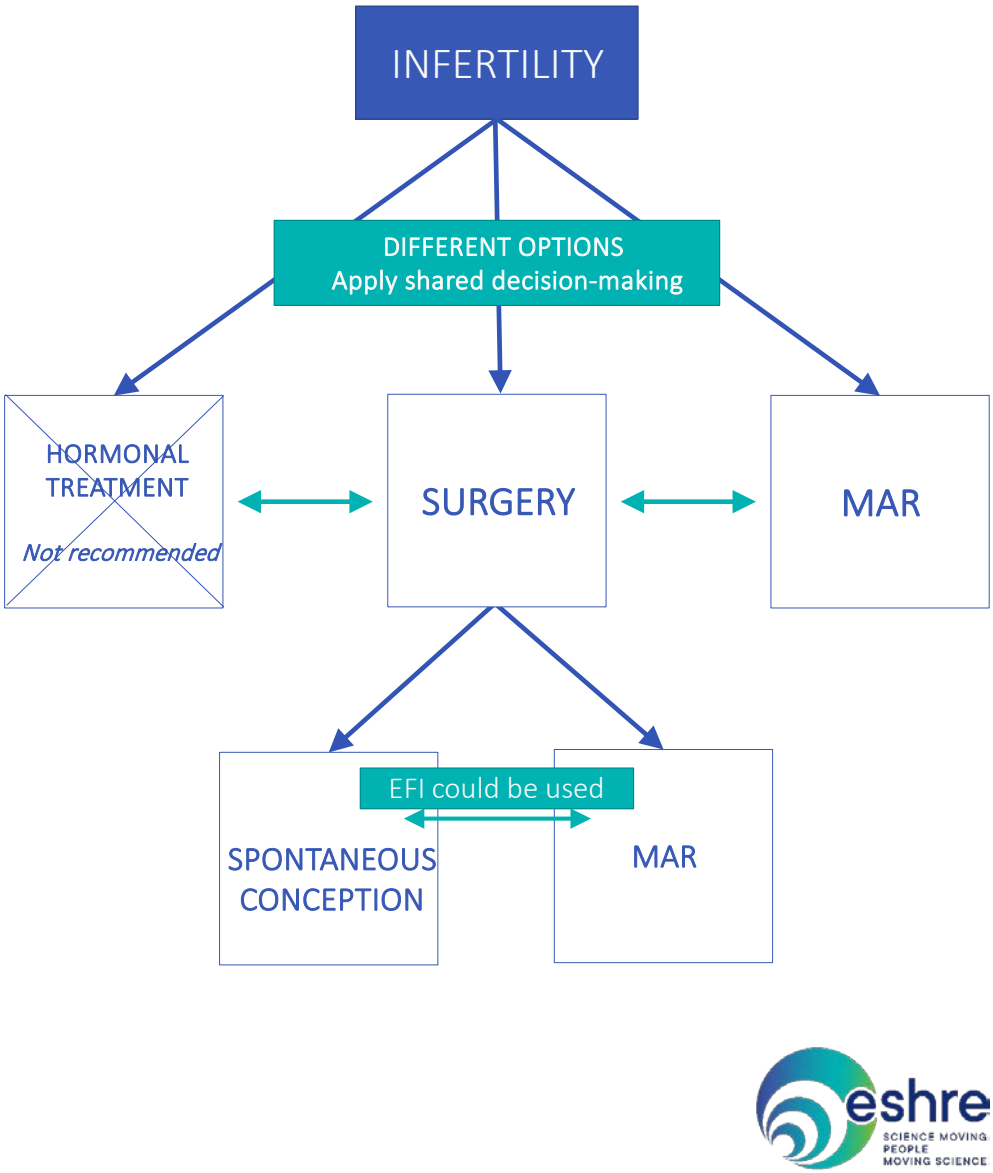


Options hormone treatme	Considerations
Combined hormonal contracept	• Oral, vaginal ring, or transdermal • Continuous use can be considered
Progestogens	• Oral medication (e.g., progesterone-only pill), levonorgestrel-releasing intrauterine system or etonogestrel-releasing subdermal implant • Side effect profiles need to be considered
GnRH agonists	• As second-line treatment, based on sideeffect profile • Consider combined hormone addback therapy to prevent bone loss and hypoestrogenic symptoms
GnRH antagonists	• As second-line treatment • Evidence is limited regarding dosage or duration of treatment, and the need for add-back therapy • Considerable side effects, including potential impact on bone density
Aromatase inhibitors	• As second/third line treatment • For pain, refractory to other medical or surgical treatment • Must be combined with any of the above in reproductiveage women

NON-PHARMACOLOGICAL TREATMENTS FOR PAIN?

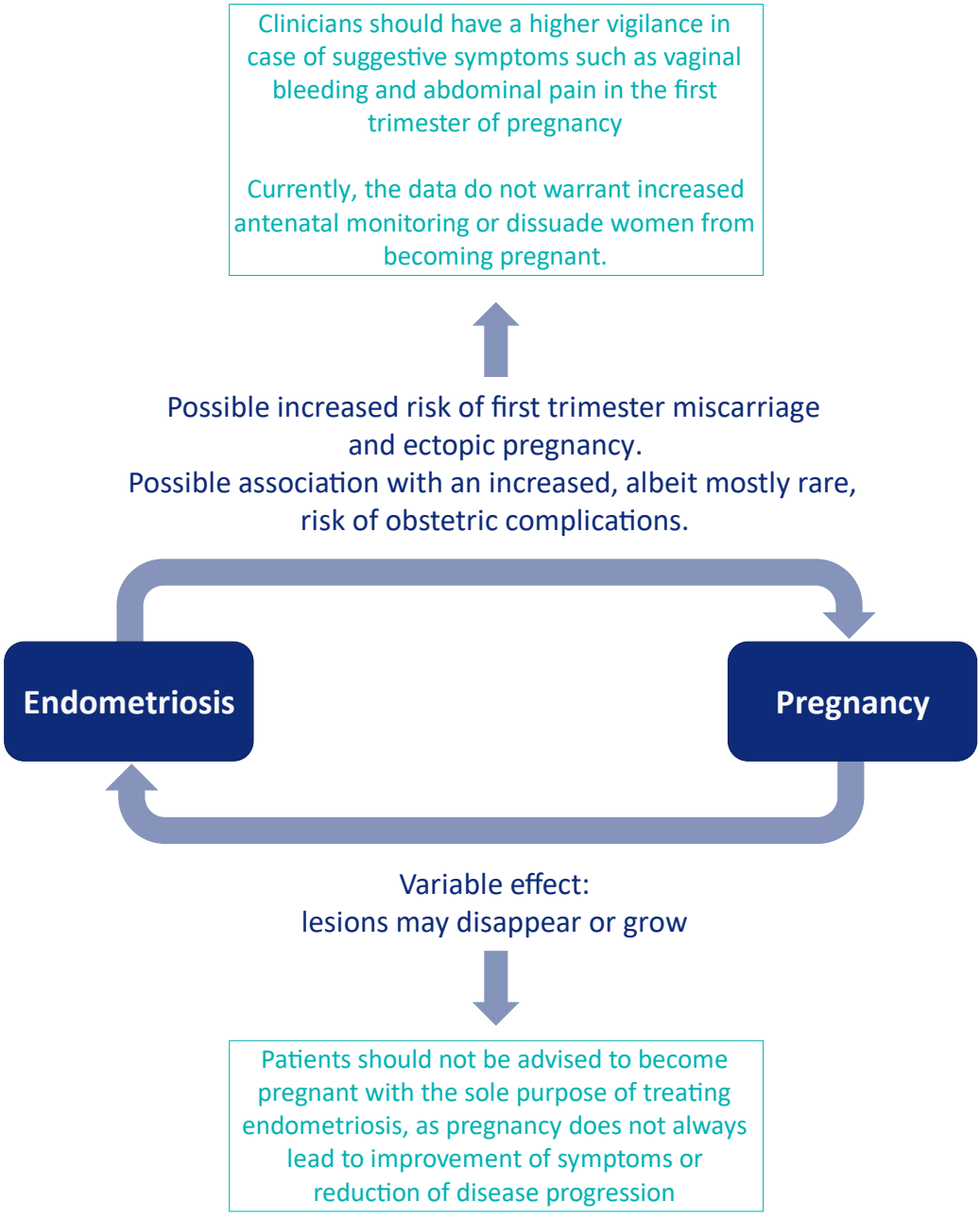
Discuss non -medical strategies to address quality of life and well -being.
No recommendation can be made for a specific intervention

TREATMENTS FOR ENDOMETRIOSIS



EFI, Endometriosis Fertility Index; MAR, medically assisted reproduction

ENDOMETRIOSIS AND PREGNANCY



Annex 6: Stakeholder review

The guideline draft was published for review for 6 weeks, between 24 June and 15 August 2021. All reviewers, their comments and the reply of the guideline development group are summarised in a review report, which is published on the ESHRE website as supporting documentation to the guideline (Annex 6). The list of representatives of professional organisation, and of individual experts that provided comments to the guideline are summarised below.

Representatives of professional organisations

Organisation	Country	Representative
The Centre for Reproduction Research, De Montfort University, UK	UK	Caroline Law and colleagues
Ferring pharmaceuticals	Denmark	
Gedeon Richer, Myovant and Pfizer		Thierry Schulmann
Department of Fertility and Gynecology, UMC Utrecht	The Netherlands	

Individual experts

Reviewer	Country
Alain Rico	France
Svetlana Dubrovina	Russia
B.C. Schoot	The Netherlands
Celine Bafort	Belgium
Astrid Cantineau	The Netherlands
Linda Giudice	USA
Fleur Blok	The Netherlands
Carlos Calhaz-Jorge	Portugal
Mukhri Hamdan	Malaysia
Velja Mijatovic, Lisette vd Houwen, Anneke Schreurs, Astrid Cantineau on behalf of the COPIE study group	The Netherlands
Pauline de Heer	The Netherlands
Aboubakr Mohamed Elnashar	Egypt
George Pados	Greece
Helen McLaughlin	UK
Ellen Klinkert	The Netherlands
Julie Prilling	

The full Annex 6: stakeholder review report is available as a separate document

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