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ESHRE guideline: endometriosis†

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STUDY QUESTION: How should endometriosis be diagnosed and managed based on the best available evidence from published literature?

SUMMARY ANSWER: The current guideline provides 109 recommendations on diagnosis, treatments for pain and infertility, management of disease recurrence, asymptomatic or extrapelvic disease, endometriosis in adolescents and postmenopausal women, prevention and the association with cancer.

WHAT IS KNOWN ALREADY: Endometriosis is a chronic condition with a plethora of presentations in terms of not only the occurrence of lesions, but also the presence of signs and symptoms. The most important symptoms include pain and infertility.

STUDY DESIGN, SIZE, DURATION: The guideline was developed according to the structured methodology for development of ESHRE guidelines. After formulation of key questions by a group of experts, literature searches and assessments were performed. Papers published up to 1 December 2020 and written in English were included in the literature review.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Based on the collected evidence, recommendations were formulated and discussed within specialist subgroups and then presented to the core guideline development group (GDG) until consensus was reached. A stakeholder review was organized after finalization of the draft. The final version was approved by the GDG and the ESHRE Executive Committee.

MAIN RESULTS AND THE ROLE OF CHANCE: This guideline aims to help clinicians to apply best care for women with endometriosis. Although studies mostly focus on women of reproductive age, the guideline also addresses endometriosis in adolescents and postmenopausal women. The guideline outlines the diagnostic process for endometriosis, which challenges laparoscopy and histology as gold standard diagnostic tests. The options for treatment of endometriosis-associated pain symptoms include analgesics, medical treatments and surgery. Non-pharmacological treatments are also discussed. For management of endometriosis-associated infertility, surgical treatment and/or medically assisted reproduction are feasible. While most of the more recent studies confirm previous ESHRE recommendations, there are five

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topics in which significant changes to recommendations were required and changes in clinical practice are to be expected.

LIMITATIONS, REASONS FOR CAUTION: The guideline describes different management options but, based on existing evidence, no firm recommendations could be formulated on the most appropriate treatments. Also, for specific clinical issues, such as asymptomatic endometriosis or extrapelvic endometriosis, the evidence is too scarce to make evidence-based recommendations.

WIDER IMPLICATIONS OF THE FINDINGS: The guideline provides clinicians with clear advice on best practice in endometriosis care, based on the best evidence currently available. In addition, a list of research recommendations is provided to stimulate further studies in endometriosis.

STUDY FUNDING/COMPETING INTEREST(S): The guideline was developed and funded by ESHRE, covering expenses associated with the guideline meetings, with the literature searches and with the dissemination of the guideline. The guideline group members did not receive payments. C.M.B. reports 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). A.B. reports grants from FEMaLE executive board member and European Commission Horizon 2020 grant; consulting fees from Ethicon Endo Surgery, Medtronic; honoraria for lectures from Ethicon; and support for meeting attendance from Gedeon Richter; A.H. reports grants from MRC, NIHR, CSO, Roche Diagnostics, Astra Zeneca, Ferring; Consulting fees from Roche Diagnostics, Nordic Pharma, Chugai and Benevolent AI 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. O.H. reports consulting fees and speaker's fees from Gedeon Richter and Bayer AG; support for attending meetings from Gedeon-Richter, and leadership roles at the Finnish Society for Obstetrics and Gynecology and the Nordic federation of the societies of obstetrics and gynecology. L.K. reports 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). M.K. reports 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. A.N. reports 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 of the World Endometriosis Society. E.S. reports 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. C.T. reports 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 and Merck SA. The other authors have no conflicts of interest to declare.

DISCLAIMER: This guideline represents the views of ESHRE, which were achieved after careful consideration of the scientific evidence available at the time of preparation. In the absence of scientific evidence on certain aspects, a consensus between the relevant ESHRE stakeholders has been obtained.

Adherence to these clinical practice guidelines does not guarantee a successful or specific outcome, nor does it establish a standard of care. Clinical practice guidelines do not replace the need for application of clinical judgement to each individual presentation, nor variations based on locality and facility type.

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Key words: endometriosis / guideline / fertility / pelvic pain / adolescent / surgery / ESHRE guideline

WHAT DOES THIS MEAN FOR PATIENTS?

Endometriosis is a chronic condition with a large impact not only on the patient's quality of life, but also on social contacts and work. Endometriosis is characterized mainly by symptoms of pain (often linked to the menstrual cycle) and infertility. Often, endometriosis is subdivided according to the type and location of the lesions into peritoneal endometriosis, deep endometriosis and endometrioma.

The current paper summarizes the ESHRE guideline on endometriosis, providing clinicians with evidence-based recommendations on the diagnosis and management of endometriosis-associated symptoms, including medical treatment, surgery and assisted reproduction. Information and recommendations are also provided on other topics related to endometriosis, such as prevention, pregnancy and cancer.

Introduction

Endometriosis is a disease characterized 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). The exact prevalence of endometriosis is unknown, but estimates range from 2% to 10% within the general female population and up to 50% in infertile women (Eskenazi and Warner, 1997; Meuleman *et al.*, 2009; Zondervan *et al.*, 2020).

The ESHRE Guideline for the Diagnosis and Treatment of Endometriosis (2005) and the ESHRE Guideline: Management of women with endometriosis (2013) have been a reference point for best clinical care in endometriosis for years (Kennedy *et al.*, 2005; Dunselman *et al.*, 2014). Based on continuous new research and developments, it was considered that the last recommendations formulated in 2013/2014 required a revision.

Materials and methods

The guideline was developed according to a well-documented methodology that is universal to ESHRE guidelines (Vermeulen *et al.*, 2019). The core guideline development group (GDG) was composed of past members of the guideline group from 2013 and additional experts selected from applicants to a call for experts. All other European experts applying to the call were included as subgroup members, assisting a core group member preparing the guideline on a certain topic. The GDG included two patient representatives, and five patient organizations were represented in the subgroups.

Forty-two key questions were formulated by the GDG, of which seven were answered as narrative questions, and 35 as PICO (Patient, Intervention, Comparison, Outcome) questions. For each PICO question, databases (PubMed/MEDLINE and the Cochrane library) were searched from inception to 1 December 2020, limited to studies written in English. From the literature searches, studies were selected based on the PICO questions, assessed for quality and summarized in evidence tables. GDG subgroup meetings were organized, face-to-face and online, for presentation and discussion of the evidence and draft recommendations by the assigned core group member. Proposed recommendations by the subgroups were then discussed in core group meetings until a consensus was reached. Each recommendation was labelled as strong or weak and a grade was assigned based on the strength of the supporting evidence (High ⊕⊕⊕⊕, Moderate ⊕⊕⊕◯, Low ⊕⊕◯◯ and Very low ⊕◯◯◯). Good practice points (GPPs) based on clinical expertise were added where relevant to clarify the recommendations or to provide further practical advice. 'Research only' recommendations were also made, and those interventions should be applied only within the context of research, with appropriate precautions and ethical approval.

Strong recommendations should be used as a recommendation to be applied for most patients, while weak recommendations require discussion and shared decision-making (Fig. 1).

For the narrative questions, a similar literature search was conducted. Collected data were summarized in a narrative summary and conclusions were formulated. In case of insufficient data to provide recommendations in reply to a PICO question, a conclusion was also added. For clarity, these conclusions are labelled 'conclusion, not recommendation' in the current paper.

The guideline draft and an invitation to participate in the stakeholder review were published on the ESHRE website between 24 June and 15 August 2021. All comments were processed by the core group, either by adapting the content of the guideline and/or by replying to the reviewer. The review process was summarized in the review report, which is published on the ESHRE website (www.eshre.eu/Guidelines). Overall, 56.5% of the 253 comments resulted in an adaptation or correction in the guideline text.

This guideline will be considered for update 4 years after publication, with an intermediate assessment of the need for updating 2 years after publication.

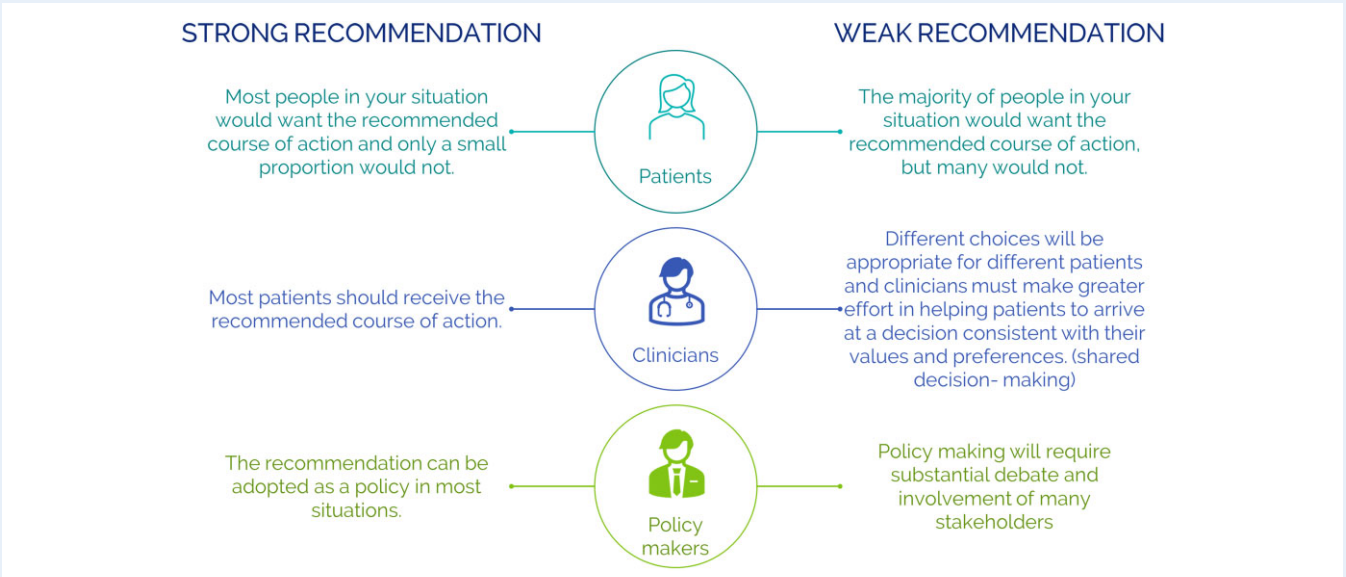

Figure 1. Suggested interpretation of strong and weak recommendations by patients, clinicians and health care policy makers.

Results

Key questions and recommendations

The scope of the ESHRE guideline on endometriosis is to provide guidance on the management of endometriosis; either diagnosed or strongly suspected. In line with endometriosis research, terminology and discussion, the guideline is focused on females and menstruation. The GDG recognizes 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. Throughout, the term 'women with endometriosis' is used, but this is not intended to isolate, exclude or diminish any individual's experience nor to discriminate against any group.

Diagnosis of endometriosis

The recommended diagnostic process for endometriosis is summarized in Fig. 2.

Can clinical symptoms predict the presence of endometriosis?

The GDG recommends that clinicians should consider the diagnosis of endometriosis in individuals presenting with the following cyclical and non-cyclical signs and symptoms: dysmenorrhoea, 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 (Forman *et al.*, 1993; Eskenazi *et al.*, 2001; Ballard *et al.*, 2008; Nnoaham *et al.*, 2012).	GPP

Does the use of symptom diaries or questionnaires compared to traditional history taking lead to improved or earlier diagnosis of endometriosis?

As no recommendation could be made, the following conclusion was formulated. 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 *(conclusion, not recommendation)*.

Does clinical examination of symptomatic women reliably predict the presence of endometriosis?

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 (Ripps and Martin, 1992; Nezhat *et al.*, 1994; Koninckx *et al.*, 1996; Eskenazi *et al.*, 2001; Chapron *et al.*, 2002; Condous *et al.*, 2007; Bazot *et al.*, 2009; Khawaja *et al.*, 2009; Hudelist *et al.*, 2011; Paulson and Paulson, 2011).	Strong recommendation ⊕◯◯◯
In women with suspected endometriosis, further diagnostic steps, including imaging, should be considered even if the clinical examination is normal.	Strong recommendation ⊕⊕◯◯

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

Clinicians should not use measurement of biomarkers in endometrial tissue, blood, menstrual or uterine fluids to diagnose endometriosis (Mol *et al.*, 1998; May *et al.*, 2010; May *et al.*, 2011; Liu *et al.*, 2015; Cosar *et al.*, 2016; Gupta *et al.*, 2016; Hirsch *et al.*, 2016; Nisenblat *et al.*, 2016a; Vanhie *et al.*, 2019; Moustafa *et al.*, 2020).	Strong recommendation ⊕⊕⊕◯
Clinicians are recommended to use imaging (ultrasound (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 (Bazot *et al.*, 2009; Manganaro *et al.*, 2012; Guerriero *et al.*, 2014; Thomeer *et al.*, 2014; Nisenblat *et al.*, 2016b; Moura *et al.*, 2019).	Strong recommendation ⊕⊕◯◯
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

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

As there is no evidence of superiority of either approach (Chapron *et al.*, 1998; Byrne *et al.*, 2018; Bafort *et al.*, 2020), the GDG concluded that both diagnostic laparoscopy and imaging combined with empirical treatment (hormonal contraceptives or progestogens) can be considered in women suspected of endometriosis. Pros and cons should be discussed with the patient *(conclusion, not recommendation)*.

Is long-term monitoring of women with endometriosis beneficial in preventing adverse outcomes (recurrence, complications, malignancy)?

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 (Pittaway, 1990; Matalliotakis *et al.*, 1994; Chen *et al.*, 1998).	Weak recommendation ⊕◯◯◯
The appropriate frequency and type of follow-up or monitoring is unknown and should be individualized based on previous and current treatments, and severity of the disease and symptoms.	GPP

Does early diagnosis of endometriosis versus late diagnosis lead to better quality of life?

Although no adequate studies exist to support the benefits of early versus late diagnosis, the GDG recommends that in symptomatic women,

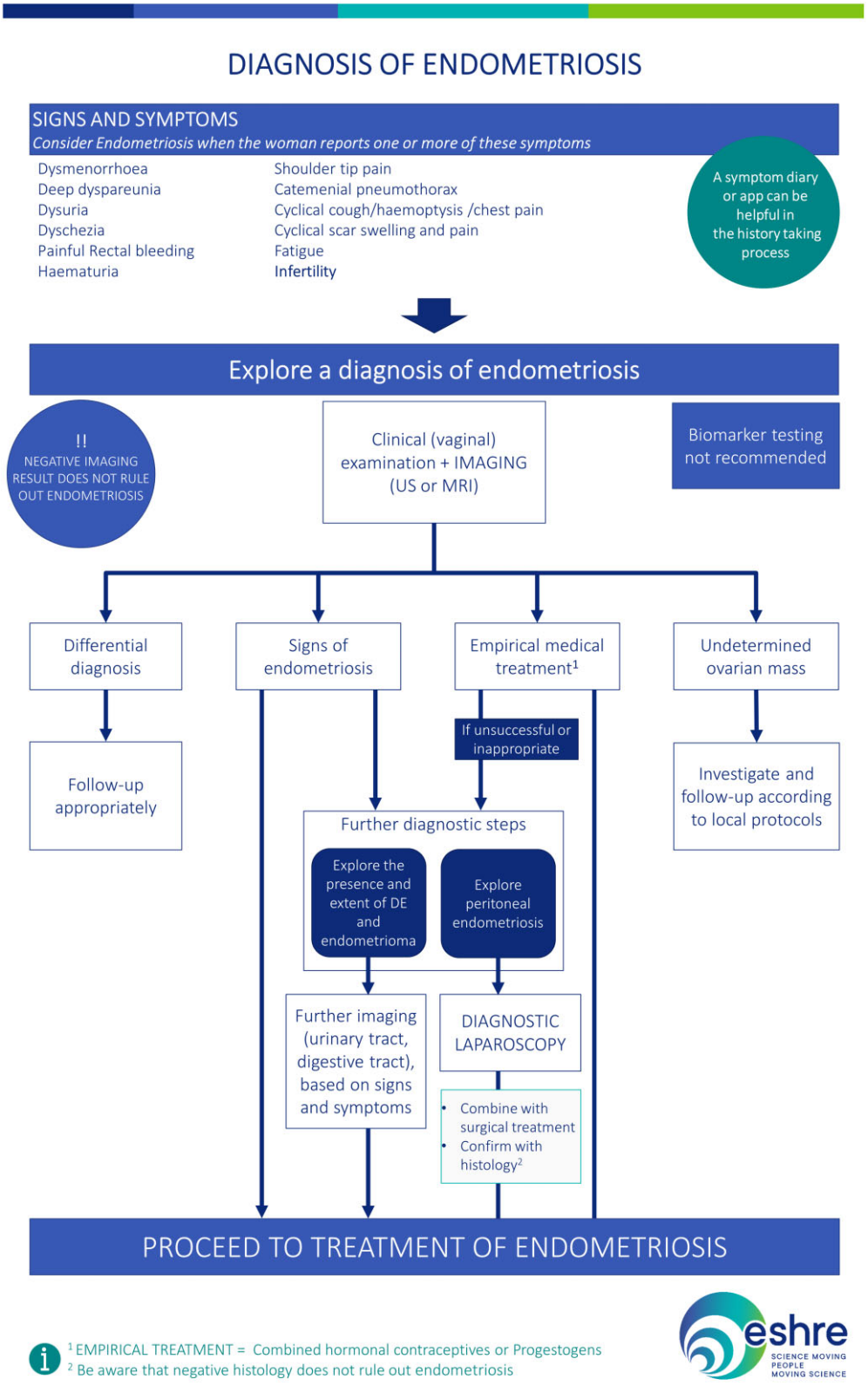

Figure 2. The recommended diagnostic process for endometriosis. DE, deep endometriosis; US, ultrasound.

attempts should be made to relieve symptoms, either by empirical treatment or after a diagnosis of endometriosis *(conclusion, not recommendation)*.

Treatment of endometriosis-associated pain

The recommendations for treatment of pain symptoms linked to endometriosis are summarized in Fig. 3.

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

Women may be offered non-steroidal anti-inflammatory drugs (NSAIDs) or other analgesics (either alone or in combination with other treatments) to reduce endometriosis-associated pain (Brown *et al.*, 2017).	Weak recommendation ⊕○○○

Are hormone therapies effective for painful symptoms associated with endometriosis?

It is recommended to offer women hormone treatment (combined hormonal contraceptives, progestogens, GnRH agonists or GnRH antagonists) as one of the options to reduce endometriosis-associated pain.	Strong recommendation ⊕⊕⊕○
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
It is recommended to prescribe women a combined hormonal contraceptive (oral, vaginal ring or transdermal) to reduce endometriosis-associated dyspareunia, dysmenorrhoea and non-menstrual pain (Brown *et al.*, 2018; Jensen *et al.*, 2018; Grandi *et al.*, 2019).	Strong recommendation ⊕⊕○○
Women suffering from endometriosis-associated dysmenorrhoea can be offered the continuous use of a combined hormonal contraceptive pill (Hee *et al.*, 2013; Zorbas *et al.*, 2015; Muzii *et al.*, 2016b).	Weak recommendation ⊕⊕○○
It is recommended to prescribe women progestogens to reduce endometriosis-associated pain (Momoeda *et al.*, 2009; Brown *et al.*, 2012; Petraglia *et al.*, 2012; Andres *et al.*, 2015; Dragoman and Gaffield, 2016).	Strong recommendation ⊕⊕○○
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 (LNG-IUS) system or an etonogestrel-releasing subdermal implant to reduce endometriosis-associated pain (Lan *et al.*, 2013; Margatho *et al.*, 2020).	Strong recommendation ⊕⊕⊕○
It is recommended to prescribe women GnRH agonists to reduce endometriosis-associated pain, although evidence is limited regarding dosage or duration of treatment (Brown *et al.*, 2010; Tang *et al.*, 2017).	Strong recommendation ⊕⊕○○
The GDG recommends that GnRH agonists are prescribed as second-line (e.g. 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 hypo-oestrogenic symptoms (Wu *et al.*, 2014; Sauerbrun-Cutler and Alvero, 2019).	Strong recommendation ⊕⊕⊕○
It can be considered to prescribe women GnRH antagonists to reduce endometriosis-associated pain, although evidence is limited regarding dosage or duration of treatment (Taylor *et al.*, 2017; Donnez *et al.*, 2020; Osuga *et al.*, 2021).	Weak recommendation ⊕⊕⊕○
The GDG recommends that GnRH antagonists are prescribed as second-line (e.g. if hormonal contraceptives or progestogens have been ineffective) owing to their side effect profile.	GPP
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 (Ferrero *et al.*, 2011; Almassinokiani *et al.*, 2014; Agarwal and Foster, 2015).	Strong recommendation ⊕⊕○○

Is surgery effective for treatment of pain associated with endometriosis?

It is recommended to offer surgery as one of the options to reduce endometriosis-associated pain (Sutton *et al.*, 1994; Franck *et al.*, 2018; Arcoverde *et al.*, 2019; Bafort *et al.*, 2020).	Strong recommendation ⊕⊕○○
When surgery is performed, clinicians may consider excision instead of ablation of endometriosis to reduce endometriosis-associated pain (Wright *et al.*, 2005; Healey *et al.*, 2014; Pundir *et al.*, 2017).	Weak recommendation ⊕⊕○○

It can be concluded that laparoscopic uterosacral nerve ablation (LUNA) is not beneficial as an additional procedure to conventional laparoscopic surgery for endometriosis, as it offers no additional benefit over surgery alone (Proctor *et al.*, 2005). Presacral neurectomy (PSN) is beneficial for treatment of endometriosis-associated midline pain as an adjunct to conventional laparoscopic surgery, but it should be stressed that PSN requires a high degree of skill and is associated with an increased risk of adverse effects such as intraoperative bleeding, and postoperative constipation, urinary urgency and painless first stage of labour (Miller *et al.*, 2020) *(conclusion, not recommendation)*.

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 (Hart *et al.*, 2008; Candiani *et al.*, 2020).	Strong recommendation ⊕⊕○○
When performing surgery in women with ovarian endometrioma, clinicians can consider both cystectomy and CO_2 laser vaporization, 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 (Muzii *et al.*, 2005, 2016a; Mossa *et al.*, 2010; Porpora *et al.*, 2010; Carmona *et al.*, 2011; Shaltout *et al.*, 2019).	Weak recommendation ⊕○○○
When performing surgery for ovarian endometrioma, specific caution should be used to minimize ovarian damage (Busacca *et al.*, 2006; Muzii *et al.*, 2015; Muzii *et al.*, 2016a; Shaltout *et al.*, 2019; Younis *et al.*, 2019).	Strong recommendation ⊕○○○

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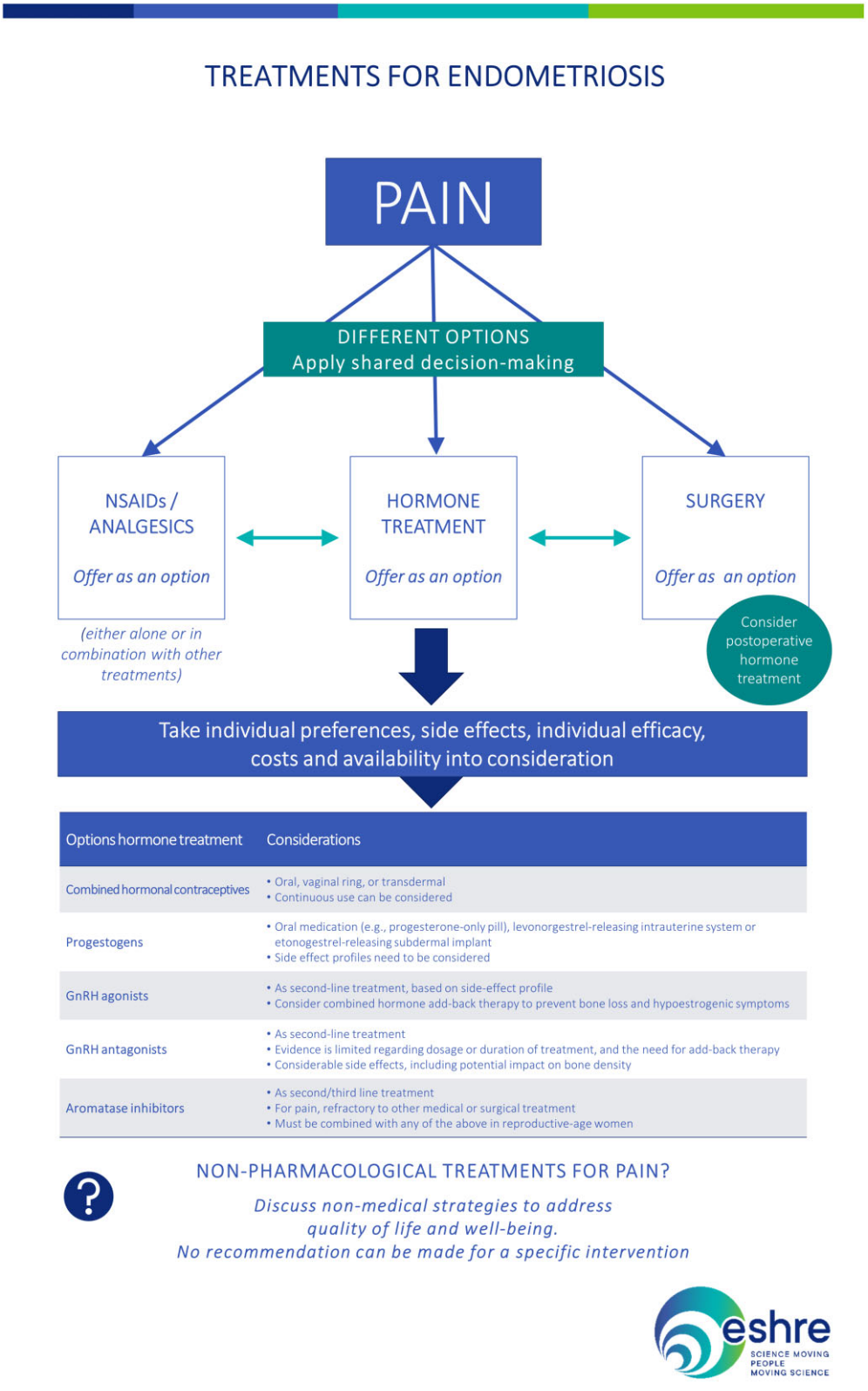

Figure 3. Summary of the recommendations for treatment of pain symptoms linked to endometriosis. NSAID, non-steroidal anti-inflammatory.

Clinicians can consider performing surgical removal of deep endometriosis, as it may reduce endometriosis-associated pain and improves quality of life (Stepniewska *et al.*, 2010; De Cicco *et al.*, 2011; Meuleman *et al.*, 2011; Byrne *et al.*, 2018; Arcoverde *et al.*, 2019; Bendifallah *et al.*, 2020).	Weak recommendation ⊕⊕◯◯
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 of potential risks, benefits and long-term effect on quality of life.	GPP

Owing 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 *(conclusion, not recommendation)*.

Is there a subgroup of women with confirmed endometriosis who respond better to surgery than others?

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.	Weak recommendation ⊕⊕◯◯
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 (Namnoum *et al.*, 1995; Sandström *et al.*, 2020; Shakiba *et al.*, 2008).	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. In the absence of prognostic markers, no recommendation could be formulated *(conclusion, not recommendation)*.

Are medical therapies effective as an adjunct to surgical therapy?

It is not recommended to prescribe preoperative hormone treatment to improve the immediate outcome of surgery for pain in women with endometriosis (Chen *et al.*, 2020).	Strong recommendation ⊕⊕◯◯
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 (Tanmahasamut *et al.*, 2012; Chen *et al.*, 2020).	Weak recommendation ⊕⊕◯◯

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

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

What non-medical management strategies are effective for symptoms associated with endometriosis (pain and quality of life)?

The GDG recommends that clinicians discuss non-medical strategies to address quality of life and psychological well-being of 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

The recommendations for treatment of endometriosis-associated infertility are summarized in Fig. 4.

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

In infertile women with endometriosis, clinicians should not prescribe ovarian suppression treatment to improve fertility (Hughes *et al.*, 2007).	Strong recommendation ⊕⊕◯◯
Women seeking pregnancy should not be prescribed postoperative hormone suppression with the sole purpose to enhance future pregnancy rates (Chen *et al.*, 2020).	Strong recommendation ⊕⊕◯◯
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 (Chen *et al.*, 2020).	Weak recommendation ⊕⊕◯◯
In infertile women with endometriosis, clinicians should not prescribe pentoxifylline, other anti-inflammatory drugs or letrozole outside ovulation-induction to improve natural pregnancy rates (Alborzi *et al.*, 2011; Lu *et al.*, 2012).	Strong recommendation ⊕◯◯◯

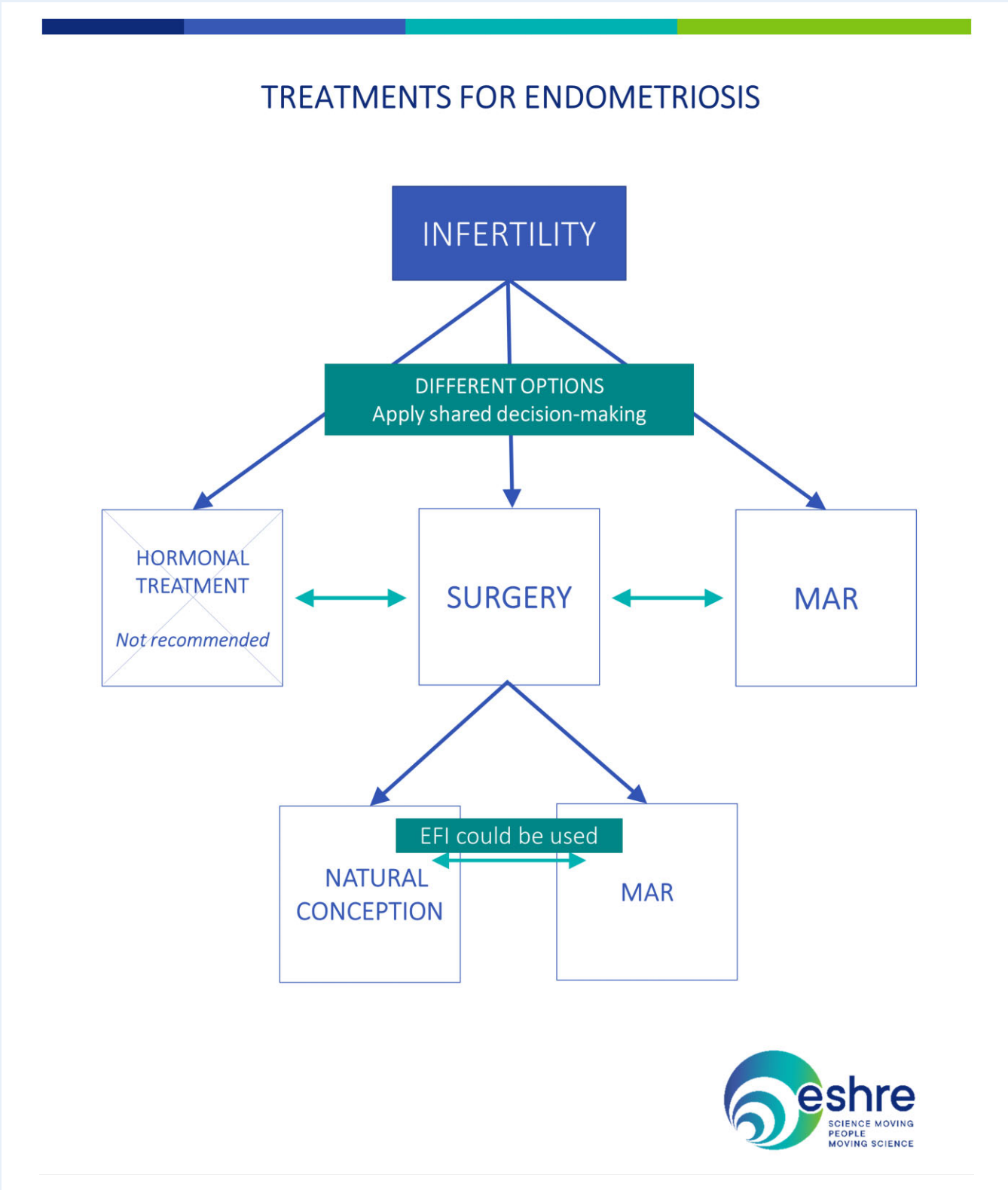

Figure 4. Summary of the recommendations on treatment of endometriosis-associated infertility. EFI, endometriosis fertility index; MAR, medically assisted reproduction.

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

Operative laparoscopy could be offered as a treatment option for endometriosis-associated infertility in revised American Society for Reproductive Medicine (rASRM) stage I/II endometriosis as it improves the rate of ongoing pregnancy (Jin and Ruiz Beguerie, 2014; Bafort *et al.*, 2020; Hodgson *et al.*, 2020).	Weak recommendation ⊕⊕◯◯
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 (Dan and Limin, 2013; Alborzi *et al.*, 2019; Candiani *et al.*, 2020).	Weak recommendation ⊕◯◯◯
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 (Meuleman *et al.*, 2011; Vercellini *et al.*, 2012; Iversen *et al.*, 2017).	Weak recommendation ⊕◯◯◯
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 the estimated endometriosis fertility index (EFI).	GPP

Which patients need treatment with assisted reproduction technology after surgery?

While no recommendation could be formulated, the GDG concluded that women should be counselled of their chances of becoming pregnant after surgery. To identify patients that may benefit from ART after surgery, the 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 *(conclusion, not recommendation)*.

Is medically assisted reproduction effective for infertility associated with endometriosis?

In infertile women with rASRM stage I/II endometriosis, clinicians may perform IUI with ovarian stimulation, instead of expectant management or IUI alone, as it increases pregnancy rates (Nulsen *et al.*, 1993; Tummon *et al.*, 1997; Omland *et al.*, 1998).	Weak recommendation ⊕◯◯◯
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 (van der Houwen *et al.*, 2014).	Weak recommendation ⊕◯◯◯
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 (Harb *et al.*, 2013; Hamdan *et al.*, 2015b; Senapati *et al.*, 2016; Murta *et al.*, 2018; Muteshi *et al.*, 2018; Alshehre *et al.*, 2021).	Weak recommendation ⊕⊕◯◯
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 (Pabuccu *et al.*, 2007; Rodriguez-Purata *et al.*, 2013; Bastu *et al.*, 2014; Kolanska *et al.*, 2017; Drakopoulos *et al.*, 2018).	Weak recommendation ⊕◯◯◯
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 (Benaglia *et al.*, 2008; Somigliana *et al.*, 2019).	Weak recommendation ⊕⊕⊕◯
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

Are medical therapies effective as an adjunct to medically assisted reproduction for endometriosis-associated infertility?

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 (Georgiou *et al.*, 2019; Cao *et al.*, 2020; Kaponis *et al.*, 2020).	Strong recommendation ⊕◯◯◯
There is insufficient evidence to recommend prolonged administration of the combined oral contraceptives (COC)/progestogens as a pre-treatment to ART to increase live birth rates (de Ziegler *et al.*, 2010).	Weak recommendation ⊕◯◯◯

Are surgical therapies effective as an adjunct prior to medically assisted reproduction for endometriosis-associated infertility?

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 (Opoien *et al.*, 2011; Hamdan *et al.*, 2015b).	Strong recommendation ⊕⊕◯◯
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 (Coccia *et al.*, 2014; Hamdan *et al.*, 2015a; Nickkho-Amiry *et al.*, 2018; Şükür *et al.*, 2021).	Strong recommendation ⊕⊕◯◯
Surgery for endometrioma prior to ART can be considered to improve endometriosis-associated pain or accessibility of follicles.	GPP
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 owing to lack of randomized studies (Bianchi *et al.*, 2009; Soriano *et al.*, 2016; Bendifallah *et al.*, 2017; Breteau *et al.*, 2020).	Strong recommendation ⊕◯◯◯

What non-medical management strategies are effective for infertility associated with endometriosis?

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 *(conclusion, not recommendation)*.

(continued)

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

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 (Cobo *et al.*, 2020; Kim *et al.*, 2020).	Strong recommendation ⊕◯◯◯

What is the impact of endometriosis on pregnancy and obstetric outcomes?

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 (Leeners *et al.*, 2018).	Strong recommendation ⊕◯◯◯
Endometriomas may change in appearance during pregnancy. In case of finding an atypical endometrioma during US in pregnancy, it is recommended to refer the patient to a centre with appropriate expertise (Leone Roberti Maggiore *et al.*, 2016).	Strong recommendation ⊕◯◯◯

Complications related directly to pre-existing endometriosis lesions are rare, but probably under-reported. Such complications may be related to their decidualization, adhesion formation/stretching and endometriosis-related chronic inflammation. Although rare, they may represent life-threatening situations that may require surgical management (Leone Roberti Maggiore *et al.*, 2016; Leone Roberti Maggiore *et al.*, 2017; Lier *et al.*, 2017; Glavind *et al.*, 2018).

Clinicians should be aware that there may be an increased risk of first trimester miscarriage and ectopic pregnancy in women with endometriosis (Leone Roberti Maggiore *et al.*, 2016; Santulli *et al.*, 2016; Kohl Schwartz *et al.*, 2017; Saraswat *et al.*, 2017; Yong *et al.*, 2020).	Strong recommendation ⊕⊕◯◯
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 (Leone Roberti Maggiore *et al.*, 2016; Lalani *et al.*, 2018; Perez-Lopez *et al.*, 2018; Horton *et al.*, 2019).	Strong recommendation ⊕⊕◯◯

The recommendations and information on endometriosis and pregnancy are summarized in Fig. 5.

Endometriosis recurrence

Is there a role for secondary prevention of recurrence of disease and painful symptoms in patients treated for endometriosis?

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 dysmenorrhoea, dyspareunia and non-menstrual pelvic pain. However, the risk of reduced ovarian reserve should be taken into account.	Strong recommendation ⊕⊕◯◯
Clinicians should consider prescribing the postoperative use of a LNG-IUS system (52 mg) or a combined hormonal contraceptive for at least 18–24 months for the secondary prevention of endometriosis-associated dysmenorrhoea (Seracchioli *et al.*, 2009; Lee *et al.*, 2018; Song *et al.*, 2018; Chen *et al.*, 2020; Zakhari *et al.*, 2021).	Strong recommendation ⊕⊕◯◯
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 ⊕◯◯◯
For the prevention of recurrence of deep endometriosis and associated symptoms, long-term administration of postoperative hormone treatment can be considered.	Weak recommendation ⊕◯◯◯
Clinicians can perform ART in women with deep endometriosis, as it does not seem to increase endometriosis recurrence per se (Somigliana *et al.*, 2019).	Weak recommendation ⊕⊕⊕◯

How should patients with reoccurring endometriosis or recurring symptoms be managed? Is repetitive surgery effective for symptoms associated with endometriosis?

Any hormone treatment or surgery can be offered to treat recurring pain symptoms in women with endometriosis (Candiani *et al.*, 1991; Hornstein *et al.*, 1997; Vercellini *et al.*, 2002; Razzi *et al.*, 2007; Muzii *et al.*, 2015; Abdou *et al.*, 2018; Koshiba *et al.*, 2018; Lee *et al.*, 2018).	Weak recommendation ⊕◯◯◯

Endometriosis and adolescence

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

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 (Geysenbergh *et al.*, 2017).	Strong recommendation ⊕◯◯◯
Clinicians may consider endometriosis in young women presenting with (cyclical) absenteeism from school, or with use of oral contraceptives for treatment of dysmenorrhoea (Chapron *et al.*, 2011).	Weak recommendation ⊕◯◯◯
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, dysmenorrhoea, dyschezia, dysuria, dyspareunia; cyclical pelvic pain (Greene *et al.*, 2009; Treloar *et al.*, 2010; Vicino *et al.*, 2010; Yang *et al.*, 2012; DiVasta *et al.*, 2018).	Strong recommendation ⊕◯◯◯

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

(continued)

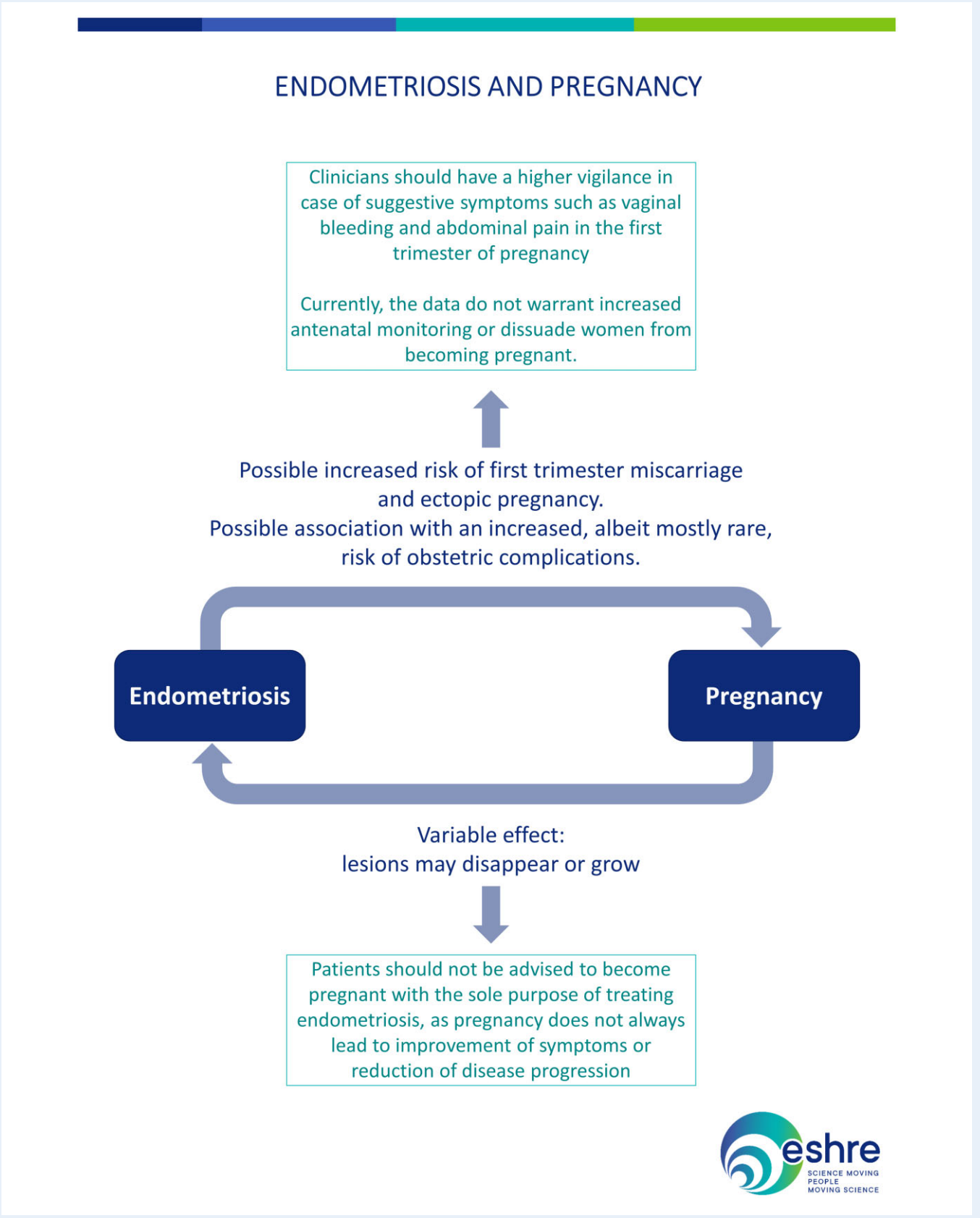

Figure 5. **Summary of the recommendations and information on endometriosis and pregnancy.**

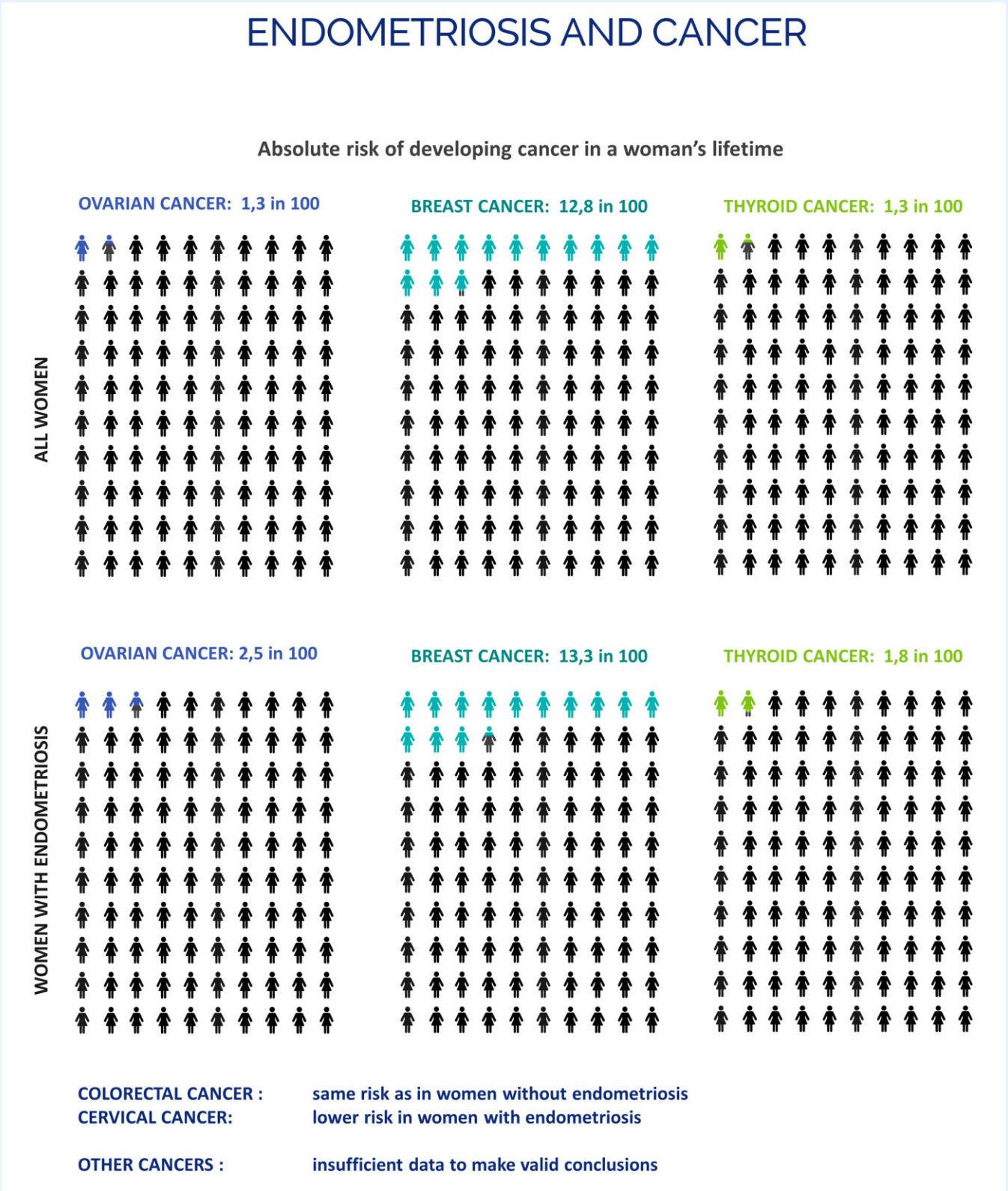

Figure 6. **Infographic on the absolute risk of developing cancer in a woman's lifetime.**

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
Transvaginal US 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 (Yang *et al.*, 2012; Brosens *et al.*, 2013; Martire *et al.*, 2020).	Strong recommendation ⊕⊕◯◯
Serum biomarkers (e.g. CA-125) are not recommended for diagnosing or ruling out endometriosis in adolescents (Seckin *et al.*, 2018; Sasamoto *et al.*, 2020).	Strong recommendation ⊕⊕◯◯
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 (Vicino *et al.*, 2010; Shah and Missmer, 2011; Yang *et al.*, 2012; Brosens *et al.*, 2013).	Weak recommendation ⊕⊕◯◯

Should diagnosis of endometriosis in adolescents be confirmed by histology?

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 (Janssen *et al.*, 2013).	Strong recommendation ⊕⊕◯◯

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

In adolescents with severe dysmenorrhoea 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 (Davis *et al.*, 2005; Yoost *et al.*, 2013; Ebert *et al.*, 2017).	Strong recommendation ⊕◯◯◯
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 (DiVasta *et al.*, 2015; Gallagher *et al.*, 2017; Gallagher *et al.*, 2018).	Weak recommendation ⊕⊕◯◯
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
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 (Roman, 2010; Tandoi *et al.*, 2011; Yeung *et al.*, 2011; Lee *et al.*, 2017).	Weak recommendation ⊕◯◯◯
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
In adolescents with endometriosis, clinicians should consider postoperative hormone therapy, as this may suppress recurrence of symptoms (Doyle *et al.*, 2009; Seo *et al.*, 2017).	Strong recommendation ⊕◯◯◯

Is endometriosis in adolescents an indication for fertility preservation (ovarian tissue/oocytes)?

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

Endometriosis and menopause

Is endometriosis still active during menopause and, if so, how should the symptoms be treated?

The GDG concluded that clinicians should be aware that endometriosis can still be active/symptomatic after menopause *(conclusion, not recommendation)*.

Is surgical/medical treatment effective and safe in women with a history of endometriosis?

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 (Redwine, 1994; Clayton *et al.*, 1999; Morotti *et al.*, 2012; Sun *et al.*, 2013; Behera *et al.*, 2006).	Weak recommendation ⊕◯◯◯
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
For postmenopausal women with endometriosis-associated pain, clinicians may consider aromatase inhibitors as a treatment option especially if surgery is not feasible (Polyzos *et al.*, 2011; Pavone and Bulun, 2012).	Weak recommendation ⊕◯◯◯

(continued)

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

Clinicians may consider combined menopausal hormone therapy for the treatment of postmenopausal symptoms in women (both after natural and surgical menopause) with a history of endometriosis (Matorras *et al.*, 2002; Gemmell *et al.*, 2017).	Weak recommendation ⊕⊕◯◯
Clinicians should avoid prescribing oestrogen-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 (Gemmell *et al.*, 2017).	Strong recommendation ⊕⊕◯◯
The GDG recommends that clinicians continue to treat women with a history of endometriosis after surgical menopause with combined oestrogen–progestogen at least up to the age of natural menopause.	GPP

Are women with endometriosis at higher risk of experiencing menopause-related major health concerns?

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 *(conclusion, not recommendation)*.

Extrapelvic endometriosis

How reliable is imaging for diagnosing extrapelvic endometriosis?

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

Does treatment for extrapelvic endometriosis relieve symptoms?

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 (Horton *et al.*, 2008; Zhu *et al.*, 2017; Andres *et al.*, 2020; Hirata *et al.*, 2020).	Weak recommendation ⊕◯◯◯
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 (Joseph and Sahn, 1996; Ceccaroni *et al.*, 2013; Nezhat *et al.*, 2014; Gil and Tulandi, 2020; Andres *et al.*, 2020; Vigueras Smith *et al.*, 2021; Ciriaco *et al.*, 2022).	Weak recommendation ⊕◯◯◯

Asymptomatic endometriosis

Is treatment beneficial for incidental finding of asymptomatic endometriosis?

The GDG recommends that clinicians should inform and counsel women about any incidental finding of endometriosis.	GPP
Clinicians should not routinely perform surgical excision/ablation for an incidental finding of asymptomatic endometriosis at the time of surgery (Moen and Stokstad, 2002).	Strong recommendation ⊕◯◯◯
Clinicians should not prescribe medical treatment in women with incidental finding of endometriosis.	Strong recommendation ⊕◯◯◯

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

Routine US monitoring of asymptomatic endometriosis can be considered (Maouris, 1991; Alcázar *et al.*, 2005; Pearce *et al.*, 2012; Serati *et al.*, 2013).	Weak recommendation ⊕◯◯◯

Primary prevention of endometriosis

Is there a role for primary prevention of endometriosis?

Although there is no direct evidence of benefit in preventing endometriosis in the future, women can be advised of aiming for a healthy lifestyle and diet, with reduced alcohol intake and regular physical activity (Hansen and Knudsen, 2013; Parazzini *et al.*, 2013a,b; Bravi *et al.*, 2014; Ricci *et al.*, 2016; Harris *et al.*, 2018; Nodler *et al.*, 2020; Qiu *et al.*, 2020).	Weak recommendation ⊕⊕◯◯
The usefulness of hormonal contraceptives for the primary prevention of endometriosis is uncertain (Vercellini *et al.*, 2011).	Weak recommendation ⊕⊕◯◯
Genetic testing in women with suspected or confirmed endometriosis should only be performed within a research setting.	RESEARCH-ONLY

Endometriosis and cancer

Are patients with endometriosis at increased risk of cancer?

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 (Fig. 6). 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 (Kvaskoff *et al.*, 2021).	Strong recommendation ⊕⊕◯◯

What information could clinicians provide to women with endometriosis regarding their risk of developing cancer?

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

Are somatic mutations in deep endometriosis of patients without cancer predictive for ovarian cancer development and/or progression?

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 *(conclusion, not recommendation)*.

Does the use of hormone treatments increase the risk of cancer?

Clinicians should reassure women with endometriosis about the risk of malignancy associated with the use of hormonal contraceptives (Smith *et al.*, 2003; Zucchetto *et al.*, 2009; Gierisch *et al.*, 2013; Havrilesky *et al.*, 2013; Braganza *et al.*, 2014; Berlanda *et al.*, 2016; Wentzensen *et al.*, 2016; Butt *et al.*, 2018; Michels *et al.*, 2018).	Strong recommendation ⊕○○○

Should women with endometriosis be monitored for detection of malignancy?

In women with endometriosis, clinicians should not systematically perform cancer screening beyond the existing population-based cancer screening guidelines (Kvaskoff *et al.*, 2021).	Strong recommendation ⊕⊕○○
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

Does surgery for endometriosis change the future risk of cancer?

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) (Rossing *et al.*, 2008; Melin *et al.*, 2013; Haraguchi *et al.*, 2016).	Strong recommendation ⊕⊕○○

Discussion

This paper provides an overview of recommendations for diagnosis of endometriosis and treatment of associated symptoms during different stages of life. In addition, guidance is provided on the possible connection with development of cancer, and with regards to prevention. Overall, 109 recommendations have been formulated, 79 supported by research data and 30 GPPs based primarily on clinical expertise. The guidelines are based on the best available evidence or, where data of sufficient quality were absent, on recommendations by the GDG (GPPs).

The current guideline and recommendations are an update of the ESHRE endometriosis guidelines published in 2013 and 2005 (Kennedy *et al.*, 2005; Dunselman *et al.*, 2014). The key questions and topics covered in the guideline of 2013 were updated based on data published between 2013 and 2021, where available, and in accordance with changes in clinical practice. The latter applied, for example, to the oral use of danazol and anti-progestogens as a medical treatment and to LUNA, PSN and anti-adhesion agents as surgical interventions. These interventions are still discussed in the guideline, but no longer discussed in recommendations for clinical practice.

While 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. The first change, primarily based on clinical practice rather than published data, is the evolution in the diagnostic process. While previously a laparoscopy was regarded as the diagnostic gold standard, it is now only recommended in patients with negative imaging results and/or where empirical treatment was unsuccessful or inappropriate. Secondly, studies on GnRH antagonist treatments support their use as an additional (second-line) treatment option. Thirdly, recent data indicate that postoperative medical treatment may be beneficial towards pain management and support a recommendation to offer it to women not desiring immediate pregnancy. Fourthly, 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 because of unclear benefits. Finally, the 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.

In addition to the topics discussed in the previous guideline, the current guideline addresses highly important previous gaps in clinical management, with an additional chapter on adolescent endometriosis, information on pregnancy and fertility preservation, and extended information on endometriosis in menopause, as well as data on the link between endometriosis and cancer.

Despite our best efforts to provide clear guidance on the management of endometriosis using all available evidence, there is still an urgent need for more research both to achieve more clarity on the most appropriate diagnostic and treatment options, and to answer very basic questions as to the natural course of the disease. This guideline provides 30 recommendations for research written to inspire researchers and hopefully also facilitate funding for endometriosis studies (Supplementary Data).

In summary, the 2022 ESHRE Guideline: Endometriosis is a comprehensive update of the existing evidence and should assist healthcare professionals in their decision making and patients in their understanding of the management suggestions. Active involvement and input by patient representatives at all stages was central to the success of this endeavour. As such, the guideline was created by medical professionals, patient representatives and specialists in epidemiology and guideline methodology. The detailed guideline document and a patient-friendly version can be accessed via the ESHRE website (https://www.eshre.eu/Guideline/Endometriosis).

Supplementary data

Supplementary data are available at *Human Reproduction Open* online.

Data availability

The full guideline and supporting data (literature report, evidence tables) are available on www.eshre.eu/guidelines.

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Authors' roles

The guideline core group was chaired by C.M.B. N.V. provided methodological support. All other authors contributed equally to writing the guideline. All authors have revised and approved the final version. The collaborators supported the guideline core group for the individual chapters.

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Conflict of interest

C.M.B. reports 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). A.B. reports grants from FEMaLE executive board member and European Commission Horizon 2020 grant; consulting fees from Ethicon Endo Surgery, Medtronic; honoraria for lectures from Ethicon; and support for meeting attendance from Gedeon Richter; A.H. reports grants from MRC, NIHR, CSO, Roche Diagnostics, Astra Zeneca, Ferring; Consulting fees from Roche Diagnostics, Nordic Pharma, Chugai and Benevolent AI 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. O.H. reports consulting fees and speaker's fees from Gedeon Richter and Bayer AG; support for attending meetings from Gedeon-Richter, and leadership roles at the Finnish Society for Obstetrics and Gynecology and the Nordic federation of the societies of obstetrics and gynecology. L.K. reports 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). M.K. reports 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. A.N. reports 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. E.S. reports 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. C.T. reports 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. The other authors have no conflicts of interest to declare.

Appendix

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