Annex 8: Evidence tables

This annex includes the evidence tables for the PICO questions included in the guideline.

QUESTION I.1 CAN CLINICAL SYMPTOMS PREDICT THE PRESENCE OF ENDOMETRIOSIS?

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Diagnostic test	Outcome measures	Effect size	Authors conclusion	Comments
(Ballard, *et al.*, 2008)	large retrospective analysis	n=5540 women matched (year-of-birth and practice) to 4 controls	Symptoms within 3 years before the diagnosis of endometriosis	Prevalence of symptoms in endometriosis vs controls	OR (95% CI) for different symptoms: abdominopelvic pain 5.2 (4.7-5.7), dysmenorrhea 8.1 (7.2-9.3), heavy menstrual bleeding 4.0 (3.5-4.5), infertility 8.2 (6.9-9.9), dyspareunia/postcoital bleeding 6.8 (5.7-8.2), urinary tract symptoms 1.2 (1.0-1.3). history of ovarian cyst 7.3 (5.7-9.4), irritable bowel syndrome 1.6 (1.3-1.8), pelvic inflammatory disease 3.0 (2.5-3.6) fibrocystic breast disease 1.4 (1.2-1.7) Increasing the number of symptoms increased the chance of having endometriosis	Specific symptoms and frequent medical consultation are associated with endometriosis and appear useful in the diagnosis.	
(Nnoaham, *et al.*, 2012)	multi-centre prospective, observational, two-phase study	Symptomatic women (n =1,396) scheduled for laparoscopy without a previous surgical diagnosis of endometriosis	clinical symptoms, medical history and pre-operative US		Menstrual dyschezia (pain on opening bowels) and a history of benign ovarian cysts most strongly predicted both any and stage III and IV endometriosis in both phases.	The best-fitting predictive model included, along with ultrasound evidence, menstrual dyschezia, ethnicity, and a history of benign ovarian cysts as the variables with the strongest predictive performance.	
(Eskenazi, *et al.*, 2001)	prospective study	90 women undergoing laparoscopy for various gynaecological indications Test sample : 120 women that underwent surgery	Index test: Symptoms (infertility and dysmenorrhea, dyspareunia, and noncyclic pelvic pain)	value for predicting endometriosis at surgery Data on US are included in question I.3	Dysmenorrhea in 16/53 (30%) no endometriosis vs 24 (65%) of 37 women with endometriosis Pelvic pain 8(15%) vs 12 (32%) Dyspareunia 12 (23%) vs 8 (22%) Infertility 11(21%) vs 5(14%)	We found that non-invasive procedures (history, pain reports, physical examination, ultrasound) have moderate success in predicting a surgical diagnosis of endometriosis. symptomatology including dysmenorrhea, pelvic pain, dyspareunia or infertility correctly classified 66% of the women.	

Reference	Study Type	Patients	Diagnostic test	Outcome measures	Effect size	Authors conclusion	Comments
(Forman, *et al.*, 1993)	prospective study	99 women undergoing laparoscopy for subfertility	Symptoms (7-point physical symptom and medical history questionnaire) (i) severe pain during menstruation, (ii) severe pelvic pain unrelated to menstruation, (iii) deep dyspareunia (iv) coloured vaginal discharge in the previous 6 months (v) past use of an IUD; (vi) a history of a previous laparotomy Reference test: laparoscopic diagnosis of endometriosis	Value for predicting endometriosis	severe dysmenorrhoea was the predictive of endometriosis (RR 1.7) Severe dysmenorrhoea, a vaginal discharge, past use of a coil and previous laparotomies were predictive for pelvic adhesions (relative risks 2.1, 3.3, 2.1,1.9, respectively).	In conclusion, patients with a history of severe dysmenorrhoea, a coloured vaginal discharge, previous use of a coil and those who have previously undergone a laparotomy are significantly more likely to have pelvic pathology than patients with a negative history	

INCLUDED AS BACKGROUND INFORMATION
(Hsu, *et al.*, 2010)

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	The evidence to predict endometriosis based on clinical symptoms alone is weak and incomplete. In women seeking help from general practitioners, a number of signs and symptoms were shown to be associated with a diagnosis of endometriosis. The guideline group suggests to consider these signs and symptoms for a diagnosis of endometriosis.
Balance between desirable and undesirable outcomes	Benefit: Earlier detection and ruling out of a common and costly disease hopefully leading to less suffering and better treatment outcomes Risks: Overtreatment in asymptomatic patients
Balance between different outcomes	It was considered that focus would be on identifying women for further diagnostic work-up rather than missing diagnosis of endometriosis due to unspecific/unfamiliar symptoms.
Patient values and preference	Na
Resource use, equity, acceptability and feasibility	Na

GOOD PRACTICE POINT	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.

QUESTION I.2 DOES THE USE OF SYMPTOM DIARIES OR QUESTIONNAIRES COMPARED TO TRADITIONAL HISTORY TAKING LEAD TO IMPROVED OR EARLIER DIAGNOSIS OF ENDOMETRIOSIS?

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Symptom diary/ questionnaire	Outcome measures	Effect size	Authors conclusion	Comments
(Jones, *et al.*, 2006)	cross-sectional postal survey	610 women with surgically confirmed endometriosis (response rate 83.9%)	Endometriosis Health Profile-30 (EHP-30) questionnaire	Na	na	Questionnaire developed to measure the health-related quality of life (HRQoL) of women with endometriosis.	Developed for therapeutic studies
(Gater, *et al.*, 2020)	Development report	review of published qualitative literature; concept elicitation interviews and cognitive interviews. The FDA and EMA as well as PRO and clinical experts were consulted throughout the process.	Endometriosis Symptom Diary (ESD) and Endometriosis Impact Scale (EIS)	Na	na	Evidence from extensive qualitative research supports the content validity of the ESD and EIS as patient-reported measures of the disease-defining symptoms of endometriosis and the associated impact on women's lives. Future research will seek to establish the measurement properties of the measures.	Developed for therapeutic studies
(Deal, *et al.*, 2010)	Development report & validation	clinician input and the results of 5 focus groups	Daily electronic Endometriosis Pain and Bleeding Diary (EPBD)	Na	na	the 17-item EPBD reliably and validly characterizes the types of pain that patients identify as being important. As a daily patient-reported assessment, it overcomes the significant potential for intra- and inter-rater variability and rater and recall bias	
(van Nooten, *et al.*, 2018)	Development report	Iterative development process, based on EPBD	patient-reported endometriosis pain daily diary (EPDD)	Na	na	The EPDD is a PRO for the evaluation of endometriosis-related pain and its associated impacts on patients' lives.	
(Wyrwich, *et al.*, 2018)	Development report & validation	8 focus groups, 20 semistructured telephone interviews, and 15 face-to-face concept elicitation and cognitive debriefing interviews	Endometriosis Daily Pain Impact Diary	Na	na	the daily dysmenorrhea and nonmenstrual pelvic pain impact items, developed and tested through qualitative research involving both focus groups and individual interviews, are well-defined, reliable, valid, and	

Reference	Study Type	Patients	Symptom diary/ questionnaire	Outcome measures	Effect size	Authors conclusion	Comments
						responsive for measuring the impact of pain in endometriosis to assess therapeutic response	
(Surrey, *et al.*, 2017)	scoping review	16 studies were identified, of which 10 described measures for endometriosis in general, 2 described measures for endometriosis at specific sites, and 4 described measures for DE	Patient-completed or symptom-based screening tools	Na	Most measures required physician, imaging, or laboratory assessments in addition to patient-completed questionnaires, and several measures relied on complex scoring. Validation for use as a screening tool in adult women with potential endometriosis was lacking in all studies, as most studies focused on diagnosis vs screening.	Review did not identify any fully validated, symptom-based, patient-reported questionnaires for endometriosis screening in adult women.	
No studies were retrieved on the use of symptom diaries/questionnaire/app compared to traditional history taking techniques and assessing outcomes of diagnosis of endometriosis, screening, triage of symptomatic patients							

INCLUDED AS BACKGROUND INFORMATION
(Haas, *et al.*, 2013, Johnson, *et al.*, 2017, Vercellini, *et al.*, 2007)

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	There is no evidence to answer the second question whether the use of symptom diaries or questionnaires compared to traditional history taking lead to improved or earlier diagnosis of endometriosis. Most publications focus on pain diaries and questionnaires for research purposes and in clinical studies.
Balance between desirable and undesirable outcomes	Benefit: Earlier detection and ruling out of a common and costly disease hopefully leading to less suffering and better treatment outcomes Risks: Overtreatment in asymptomatic patients
Balance between different outcomes	Overall earlier detection desired by patients and medical staff as there is a known long diagnostic delay in endometriosis. Symptom diaries or questionnaires may empower individuals to seek medical advice and to demonstrate/document their symptoms for wider acceptance. There may be some time constraints linked to symptom diaries or questionnaires, and they could possibly be contra-productive for detailed history taking.
Patient values and preference	Diaries and linked education on symptoms of endometriosis may empower patients in discussions with clinicians.

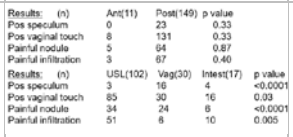
Resource use, equity, acceptability and feasibility	Inexpensive approach, but it needs standardization. There may be a difference between specialists and GPs with regards to the use and usefulness of symptom diaries or questionnaires.
RECOMMENDATION	No recommendation could be formulated with regards to the symptom diaries or questionnaires. The following statement was formulated: Although currently no evidence exists that a symptom diary/questionnaire/app reduces the time to diagnosis or 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.

QUESTION I.3 DOES CLINICAL EXAMINATION OF SYMPTOMATIC WOMEN RELIABLY PREDICT THE PRESENCE OF ENDOMETRIOSIS?

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Diagnostic test	Outcome measures	Effect size	Authors conclusion	Comments
(Bazot, *et al.*, 2009)	Retrospective longitudinal study	92 consecutive patients with clinical evidence of pelvic endometriosis Clinical presentation: dysmenorrhoea 79/92, dyspareunia 63/92, dyschezia 32/92, dysuria 3/92, infertility 21/92; history of surgery for endometriosis 31/92 Age: median 31.8 years (range 20 - 50 years)	Index test: Physical examination Reference test: laparoscopy 79/92 (85.9%), laparotomy 13/92 (14.1%) + histopathology (also evaluates TVS, RES, and MRI, performed preoperatively) DE was diagnosed when [1] lesions were visualized on the posterior vaginal fornix, [2]infiltration or a nodule was detected on vaginal examination, involving the vagina, torus uterinus, uterosacral ligaments, or pouch of Douglas, and [3] infiltration or a mass was detected on rectal digital examination, involving the rectosigmoid colon. All examinations performed by the same highly experienced gynecologist	Diagnostic accuracy (sensitivity, likelihood ratios (LR+ and LR-)	DE diagnosed at physical exam in 75/92 (81.5%) women. <u>Uterosacral ligaments</u> Sensitivity: 73.5% (61/83) Specificity: 77.8% (7/9) PPV: 96.8% (61/63) NPV: 24% (7/29) Accuracy: 73.9% (68/92) <u>Vagina</u> Sensitivity: 50% (15/30) Specificity: 87% (54/62) PPV: 65.2% (15/23) NPV: 78.3% (54/69) Accuracy: 75% (69/92) <u>Rectovaginal septum</u> Sensitivity: 18.2% (2/11) Specificity: 96.3% (78/81) PPV: 40% (2/5) NPV: 89.7% (78/87) Accuracy: 86.9% (80/92) <u>Intestine</u> Sensitivity: 46% (29/63) Specificity: 72.4% (21/29) PPV: 78.4% (29/37) NPV: 38.2% (21/55) Accuracy: 54.4% (50/92)	Physical examination is crucial for detecting DE, although it is not very accurate for specific locations.	
(Chapron, *et al.*, 2002)	Retrospective cohort study	160 women with histology proved deeply infiltrating endometriosis.	Assessment of deep endometriosis according to location and exam findings Anterior vs posterior DE Posterior (USL, Vaginal) vs Intestinal	Diagnostic accuracy		Routine clinical examination is not sufficient for diagnosing and locating DE	small sample size, tertiary centre, retrospective, continuous series
(Koninckx, *et al.*, 1996)	Retrospective / prospective study	61 women scheduled for laparoscopy + retrospective data for 140 women with DE	Index test: clinical examination during menstruation	Diagnostic accuracy	Menstrual nodularities <u>Deep endometriosis (n=13)</u> Sensitivity: 76.9 Specificity: 76.2	Clinical examination during menstruation can diagnose reliably DE, cystic ovarian	

Reference	Study Type	Patients	Diagnostic test	Outcome measures	Effect size	Authors conclusion	Comments
		+ 16 women with painful pelvic nodularities during menstruation	Reference test: laparoscopic diagnosis Bimanual pelvic exam scored positive when an induration and/or painful nodularities were felt.		Endometrioma (n=9) Sensitivity:77.8 Specificity:70.2 Severe cul-de-sac (n=12) Sensitivity: 91.7 Specificity: 77.2 DE or endometrioma or Severe cul-de-sac (n=24) Sensitivity: 79.2 Specificity:91.7	endometriosis, or cul-de-sac adhesions.	
(Nezhat*, et al.*, 1994)	Retrospective cohort study	91 laparoscopically confirmed endometriosis Age : 35 years (range 17-59 yrs)	Index test: pelvic exam Comparator test: TVUS Reference test : laparoscopy Abnormal bimanual exam = Pain, Nodularity, Enlarged Adnexae, or Abnormal Uterine Configuration	Descriptive results for pelvic exam Concordance between TVUS and physical exam	Pelvic exam Abnormal 48 (53%) Normal 43 (47%) Abnormal pelvic exam: 37 (41%) had pelvic endometrial implants with adhesions and 44 (48%) had ovarian endometriosis. In 10 women (11%) both the ovaries and uterus were involved. Concordance between TVUS and physical exam was 65%	For women with peritoneal endometriosis and adhesions , a similar diagnostic accuracy of bimanual examination and transvaginal ultrasound in women with an immobile uterus and adnexal mass or tenderness	small sample size, single examiner, poor method description
(Khawaja*, et al.*, 2009).	Retrospective cohort study	796 women for laps because of $1^0/2^0$ infertility 16.8% diagnosed with endometriosis	Index test: Physical signs Reference test: laparoscopy Physical signs: Built of patient, hyperandrogenism, number of abdominal masses, pelvic exam Single examiner	N (%) and OR for different stages of endometriosis	Association of clinical presentations of endometriosis with staging. N (%) and OR for different stages Palpation of Abdominal Mass Stage I : 3 (75.0) 1.00 Stage II: 0 (0.0) 0.0.0 Stage III: 1 (25.0) 0.79 Stage IV: 0 (0.0) 0.0.0 Tenderness Stage I : 8 (11.6) 1.00 Stage II: 7 (12.1) 1.25 Stage III: 6 (20.7) 1.99 Stage IV: 1 (6.3) 0.74 Nodularity Stage I : 4 (5.8) 1.00 Stage II: 3 (5.2) 1.07 Stage III: 3 (10.3) 1.99 Stage IV: 0 (0.0) 0.0.0 Fullness Stage I : 7 (10.1) 1.00 Stage II: 8 (13.8) 1.64 Stage III: 1 (3.4) 0.38 Stage IV: 3 (18.8) 2.52 Restricted Uterine Mobility Stage I : 1 (1.4) 1.00 Stage II: 6 (10.3) 8.59	Uterine mobility or rather a lack thereof was found as a predictive marker for surgically confirmed endometriosis	

Reference	Study Type	Patients	Diagnostic test	Outcome measures	Effect size	Authors conclusion	Comments
					Stage III: 2 (6.9) 3.53 Stage IV: 3 (18.8) 17.67		
(Paulson and Paulson, 2011).	Retrospective cohort study	284 women planned for laparoscopy (CPP, bladder pain) 78% had endometriosis, 81% had interstitial cystitis, and 61% had both concurrently.	Index test: Pelvic exam prior to laparoscopy, cystoscopy Reference test: laparoscopy Exam: anterior vaginal wall tenderness	Sensitivity, positive predictive values (PPV),	Interstitial cystitis Sensitivity: 95% PPV: 85% Endo and Interstitial cystitis Sensitivity: 93% PPV: 67% Endometriosis only Sensitivity: 17% PPV: 67%	anterior vaginal wall tenderness had a sensitivity of 17% in women with endometriosis without interstitial cystitis	small sample size, incomplete description of methods (n of examiners)
(Hudelist, *et al.*, 2011)	Retrospective cohort study	129 women with symptoms suggestive of endometriosis 83 (64%) women had histological confirmation of endometriosis, 52 (40%) of whom DE	Index test: clinical examination Reference test: Transvaginal ultrasound Reference test: Laparoscopy + histology for diagnosis Bimanual per vaginam exam was considered positive if palpable nodule or thickened area or a palpable cystic expansion with topographic-anatomical correlation to the following sites: left and/or right uterosacral ligaments, vagina, rectovaginal space, pouch of Douglas, the rectosigmoid and the urinary bladder (posterior wall). Performed prior to TVS by one of five experienced clinical examiners.	Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and positive and negative likelihood ratios (LR+andLR−)	vaginal examination for preoperative diagnosis of endometriosis Ovary - % (CI) Sensitivity: 41 (22–61) Specificity: 99 (95–100) PPV: 92 (62–100) NPV: 87 (79–92) Uterosacral ligaments Sensitivity: 50 (31–69) Specificity: 80 (71–87) PPV: 43 (26–61) NPV: 84 (75–91) Pouch of Douglas Sensitivity: 76 (53–92) Specificity: 92 (85–96) PPV: 64 (43–82) NPV: 95 (89–98) Vagina Sensitivity: 73 (39–94) Specificity: 98 (94–100) PPV: 80 (44–98) NPV: 97 (93–100) Rectovaginal space Sensitivity: 78 (40–97) Specificity: 98 (94–100) PPV: 78 (40–97) NPV: 98 (94–100) Urinary bladder Sensitivity: 25 (0–81) Specificity: 100 (96–100) PPV: 100 (1–100) NPV: 98 (93–100) Rectosigmoid Sensitivity: 39 (22–58) Specificity: 97 (93–100) PPV: 86 (57–98) NPV: 84 (75–90)	especially in patients with cystic ovarian and DE, vaginal examination alone may be insufficient to detect endometriosis prior to laparoscopy. TVS is a more useful test than is vaginal examination in detecting endometriosis in the ovaries and rectosigmoid.	Surgeon not blinded to the results of the test No bowel surgery in all women, so difficult to ascertain negative histology

Reference	Study Type	Patients	Diagnostic test	Outcome measures	Effect size	Authors conclusion	Comments
(Eskenazi, *et al.*, 2001)	Prospective cohort study	90 women (laps/lap) and 120 women (laps)	Index test: Preoperative pelvic exam prior to surgery, test phase and validation phase Positive Exam: USL scarring; Nodularity/Pain; Vag Endo Lesion; Pain/Fixed Adnexae; Fixed/Painful Uterus Reference test: laparoscopy/laparotomy Data on symptoms are included above	Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV)	Results (n=42): Sens(%) Spec (%) PPV(%) NPV(%) Pos Exam (all) 76 74 67 81 Pos Exam (OMA) 100 74 60 81 Pos Exam (non-OMA) 43 26 33 81	Non-invasive procedures (history, pain reports, physical examination, ultrasound) have moderate success in predicting a surgical diagnosis of endometriosis.	small sample size, validation study, good study design
(Condous, *et al.*, 2007)	Prospective observational cohort study.	114 consecutive women undergoing total laparoscopic hysterectomy Dataset : 75 women with complete data median age was 46 years (range 34-71 years);	preoperative bimanual pelvic examination		Histologic diagnoses included endometriosis in 22.7% (17/75 The Spearman correlations between clinical size of the uterus and the weight of the uterus, the EBL, and the operating time were 0.81, 0.33, and 0.29, respectively; that is, the 2 variables tended to increase together. These correlations were all significant (p <.0001, .0044, and .0114, respectively).	significant correlation between clinical estimate of uterine size and histologic weight of the uterus, operating time, and EBL in women undergoing laparoscopic hysterectomy. These findings are of great value in preoperative counseling in relation to the risk of bleeding and the potential need for blood transfusion, and in operating room planning.	Indirect relevance - Not for diagnosis of endometriosis?
(Ripps and Martin, 1992)	Observational study	94 consecutive patients undergoing laparoscopy/laparotomy Endometriosis in 59 (63%) of the patients	Index test: pre-op pelvic exam - preoperative focal tenderness Reference test: presence or absence of endometriosis, depth and volume of the endometrial implants and the presence of other pathology. Exam: by the same examiner, zones of focal tenderness were recorded		In 45 (76%) of patients, preop focal tenderness correlated with the presence of disease in the same zone focal tenderness for predicting presence of disease in the same zone sensitivity; 0.79 Specificity: 0.32 NPV : 0.50 PPV: 0.64	focal tenderness has limited value in predicting the stage of endometriosis, but is strongly associated with the presence of disease in the cul de sac and uterosacral ligaments. There was also significant association of tenderness with deeper and larger volumes of implants,	

INCLUDED AS BACKGROUND INFORMATION

none

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	Studies of varying set-up (prospective, retrospective), small numbers and different quality. Overall, studies indicate that the diagnostic accuracy of clinical examination is low. Quality of evidence: ⊕◯◯◯
Balance between desirable and undesirable outcomes	Benefit of clinical examination: one can see vaginal nodules; can take swabs; cervix exam; easy to do Risk: Invasive/painful; not appropriate for virgo intacta
Balance between different outcomes	If not reliable for endometriosis in general it is not helpful, but clinical exam should be part of general gynaecological routine to assess causes of symptoms
Patient values and preference	Considered variable (no data)
Resource use, equity, acceptability and feasibility	Cheap, can be done in primary setting with little investment. In certain setting, a chaperone is needed. Vaginal and/or rectovaginal examination might be inappropriate in certain situations and in adolescents. This is discussed in the justification section.
RECOMMENDATION	**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.**

The evidence (and its quality)	Although useful (as above), the diagnostic accuracy is low, and endometriosis should not be ruled out based on normal clinical exam. Diagnostic accuracy and other factors with regards to imaging are described in Q I.4 Quality of evidence: ⊕⊕◯◯ (Evidence level for this recommendation is based on the studies evaluating diagnostic accuracy of imaging techniques)
Balance between desirable and undesirable outcomes	*See imaging section*
Balance between different outcomes	*See imaging section*
Patient values and preference	*See imaging section*
Resource use, equity, acceptability and feasibility	This strategy is considered acceptable and feasible

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

QUESTION I.4 ARE MEDICAL TECHNOLOGIES RELIABLE IN DIAGNOSING ENDOMETRIOSIS AND ESTABLISHING THE EXTENT OF THE DISEASE?

INCLUDED AS BACKGROUND INFORMATION
(Becker, *et al.*, 2014, Casper, 2014, Chapron, *et al.*, 1998, Cornillie, *et al.*, 1990, Duffy, *et al.*, 2020, Fassbender, *et al.*, 2014, Fernando, *et al.*, 2013, Kazanegra, *et al.*, 2008, Rahmioglu, *et al.*, 2014, Vitonis, *et al.*, 2014, Wykes, *et al.*, 2004). (Byrne, *et al.*, 2018a).

BIOMARKERS

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(May, *et al.*, 2010)	Systematic review	161 studies Nr of patient in individual studies not mentioned	Index test: biomarkers for endometriosis in serum, plasma and urine Reference test: Visual and/or histological confirmation of endometriosis, defined as the presence of peritoneal endometriotic lesions, endometriomata and/or rectovaginal endometriotic nodules	clinical value	Sens and spec not mentioned	The search identified over 100 possible biomarkers that have been investigated; however, none of these have been clearly shown to be of clinical use. Lack of high-quality studies investigating large numbers of well-phenotyped patients	Extensive review, not possible to comment on all these markers and calculate sens spec
(May, *et al.*, 2011)	Systematic review	182 studies, number of patient not stated (Patients and controls clearly shown to have or not have endometriosis, respectively (all participants to have undergone either laparoscopy or laparotomy to confirm presence or absence of disease)	Index test: Biomarkers Reference test: Surgically confirmed endometriosis	clinical value	Sens and spec not mentioned	Nine studies of high quality In 32 studies sensitivity and specificity could be calculated Most promising markers related to nerve fibers and cell cycle Whilst no marker has conclusively been shown to diagnose endometriosis, we found several high-quality studies that identified endometrial nerve fibres and molecules involved in cell	Extensive review, No possibilities to calculate sens and spec etc for all the individual markers

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
						cycle control, cell adhesion and angiogenesis as being promising candidates for future biomarker research	
(Gupta, *et al.*, 2016)	Meta-analysis	54 studies	Index test: Endometrial biomarkers histological assessment of the neuronal marker protein gene product 9.5 (PGP 9.5) Reference test: visualisation of endometriosis at surgery (laparoscopy or laparotomy) with or without histological confirmation	Diagnostic accuracy	CYP19 (aromatase cytochrome P450) (8 studies; n=444) sens = 0.77 (0.70 to 0.85); spec = 0.74 (0.65 to 0.84) PGP 9.5 (protein gene product 9.5) (7 studies; n=361) Sens = 0.96 (0.91 to 1.00); spec = 0.86 (0.70 to 1.00) outlier study Leslie 2013 was excluded from meta-analysis CA-125 (menstrual fluid) (1 study; n=104) Sens = 0.66 (0.49 to 0.80); spec = 0.89 (0.79 to 0.96) Endometrial biomarkers assessed in a single small study are not included here	Only two of the assessed biomarkers, a neural fibre marker PGP 9.5 and hormonal marker CYP19, were assessed in sufficient number of studies to obtain meaningful results. 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	
(Liu, *et al.*, 2015)	Meta-analysis	8 studies	Index test: urinary markers Reference test: visualisation of endometriosis at surgery (laparoscopy or laparotomy) with or without histological confirmation	Diagnostic accuracy	Vascular endothelial growth factor (VEGF) or vascular endothelial growth factor-A (VEGF-A) (2 studies, n=132) Diagnostic accuracy not evaluated Urinary biomarkers assessed in a single small study are not included here	Only a few urinary biomarkers have been assessed in small numbers of individual studies providing insufficient data to perform a meta-analysis. No urinary test met the criteria of either replacement or triage test for detecting endometriosis.	
(Nisenblat, *et al.*, 2016a)	Meta-analysis	141 studies involving 15,141 participants	Index test: Blood biomarkers Reference test: visualisation of endometriosis at surgery (laparoscopy or laparotomy) with or without histological confirmation	Diagnostic accuracy	Anti-endometrial Abs (4studies; n=759) Sens = 0.81 (0.76 to 0.87); spec = 0.75 (0.46 to 1.00) IL-6 (interleukin - 6) (3 studies, n=309) Sens = 0.63 (0.52 to 0.75); spec = 0.69 (0.57 to 0.82) CA-19.9 (cancer antigen-19.9) (3 studies, n=330) Sens = 0.36 (0.26 to 0.45); spec = 0.87 (0.75 to 0.99)	Only four of the assessed biomarkers (anti-endometrial Abs (anti-endometrial autoantibodies), interleukin-6 (IL-6), CA-19.9 and CA-125) were evaluated by enough studies to provide a meaningful assessment of test accuracy. None of these tests was accurate enough to replace diagnostic	

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
					CA-125 (cancer anti-gen-125) cut-off threshold > 10-14.7 U/ml (5 studies, n=733) Sens = 0.70 (0.63 to 0.77); spec = 0.64 (0.47 to 0.82) CA-125 - cut-off > 16-17.6 U/ml (5 studies, n=430) Sens = 0.56 (0.24 to 0.88); spec = 0.91 (0.75 to 1.00) CA-125 - cut-off > 20 IU/ml (6 studies, n=1304) Sens = 0.67 (0.50 to 0.85); spec = 0.69 (0.58 to 0.80) CA-125 - cut-off > 25-26U/ml (3 studies, n=963) Sens = 0.73 (0.67 to 0.79); spec = 0.70 (0.63 to 0.77) CA-125 - cut-off > 30-33U/ml (6 studies, n=1203) Sens = 0.62 (0.45 to 0.79); spec = 0.76 (0.53 to 1.00) CA-125 - cut-off > 35-36U/ml (27 studies, n=3447) Sens = 0.40 (0.32 to 0.49); spec = 0.91 (0.88 to 0.94)	surgery. Several studies identified biomarkers that might be of value in diagnosing endometriosis, but there are too few reports to be sure of their diagnostic benefit	
(Hirsch, *et al.*, 2016)	Systematic review	22 studies (16 cohort, six case-control) with 3626 participants accuracy data pooled from 14 studies (2920 participants) using CA 125 ≥ 30 units/ml	Index test : serum CA125 (CA 125 ≥ 30 units/ml) Reference test: laparoscopy + histological confirmation	Diagnostic accuracy	CA 125 ≥ 30 units/ml Sens = 52% (95% CI 38–66%). Spec = 93% (95% CI89–95%) CA 125 for moderate or severe endometriosis Sens = 63% (95% CI 47–77%) CA 125 for minimal disease Sens = 24% (95%CI 19–32%) P-value = 0.001 vs moderate/severe	CA 125 performs well as a rule-in test facilitating expedited diagnosis and ensuring investigation and treatment can be confidently tailored for the management of endometriosis. Unfortunately, a negative test, CA 125 < 30 units/ml, is unable to rule out endometriosis.	
(Mol, *et al.*, 1998)	Systematic review	2131 patients - Mixed, subfertility and pain	Index test : CA125 Reference test: laparoscopy		Sensitivity 0.04-1.0 Specificity 0.38-1.0 summary ROC curve showed a low diagnostic performance. Likelihood ratio + 2.8	ROC curves showed that the performance of serum CA-125 measurement in the diagnosis of endometriosis grade I/IV is limited, whereas its performance for grade III/IV is better Despite its limited diagnostic performance, we believe that the routine use of serum CA-125	

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
						measurement in patients with infertility might be justified	
(Cosar, *et al.*, 2016)	case-control study.	Women with surgically diagnosed (n = 24) and without (n = 24) endometriosis.	miRNA (microarray profiling) and confirmation by means of qRT-PCR	Diagnostic accuracy - area under the ROC curve (AUC).	miR-3613-5p, miR-6755-3p were down-regulated and miR-125b-5p, miR-150-5p, miR-342-3p, miR-143-3p, miR-145-5p, miR-500a-3p, miR-451a, miR-18a-5p were up-regulated more than 10-fold in the microarray. These results were confirmed with the use of qRT-PCR. Among the differentially expressed miRNAs, miR-125b-5p expression levels had the highest AUC The maximum AUC score of 1.000 was achieved when combining miR-125b-5p, miR-451a, and miR-3613-5p with the use of a logistic regression model.	miR-125b-5p had the greatest potential as a single diagnostic biomarker.	Pilot study
(Moustafa, *et al.*, 2020)	prospective study training set + validation set	subjects with a clinical indication for gynecological surgery mean age 34.1 and 36.9 years for the endometriosis and control groups Control group: varying pathologies, with leiomyoma occurring the most often (n = 39).	serum microRNA panel Circulating miRNAs, miR-125b-5p, miR-150-5p, miR-342-3p, miR-451a, miR-3613-5p, and let-7b, were measured in serum by qPCR + An algorithm combining the expression values of these microRNAs to predict the presence or absence of endometriosis on operative findings. This algorithm was then tested in an independent data set of 48 previously identified subjects not included in the training set (24 endometriosis and 24 controls) to validate its diagnostic performance.	Feasibility as diagnostic biomarkers of endometriosis in women with gynecologic disease symptoms Diagnostic accuracy (ROC analysis)	Endometriosis: significantly higher expression levels of 4 microRNAs (miR-125b-5p, miR-150-5p, miR-342-3p, and miR-451a) and lower levels of 2 serum microRNAs (miR-3613-5p and let-7b) AUC ranging from 0.68 to 0.92. A classifier combining these microRNAs : AUC 0.94 when validated in the independent set of subjects	microRNA biomarkers can reliably differentiate between endometriosis and other gynecological pathologies with an area under the curve >0.9 across 2 independent studies.	
(Vanhie, *et al.*, 2019)	Basic research + validation cohort study	discovery cohort: 38 controls + 82 endometriosis validation cohort: 30 controls; 60 endometriosis	genome-wide miRNA expression profiling by small RNA sequencing to identify a set of plasma miRNAs with discriminative potential between patients with	Diagnostic accuracy (ROC analysis)	41 miRNAs with discriminative power and 3 models Only the model for minimal-mild endometriosis (Model 2: hsa-miR-125b-5p, hsa-miR-28-5p and hsa-miR-29a-3p) had diagnostic power above chance	miRNA-based diagnostic models for endometriosis failed the test of independent validation.	

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
		Samples from existing biobank	and without endometriosis. Expression of this set of miRNAs was confirmed by RT-qPCR. Diagnostic models were built using multivariate logistic regression with stepwise feature selection and the models were tested for validation in an independent cohort.		performance in the independent validation (AUC = 60%) with an acceptable sensitivity (78%) but poor specificity (37%).		

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	Evidence on most topics is summarized in high quality systematic reviews and meta-analysis. The studies included in the reviews/meta-analysis are low to moderate quality. Quality of evidence: ⊕⊕⊕◯
Balance between desirable and undesirable outcomes	Benefit: A non-invasive, cost-effective and reliable approach to rule in/out endometriosis would allow for individualized treatment and reduce uncertainty and unnecessary investigations and treatment attempts. Risks: Sensitivity/specificity is not sufficient for the different tests to replace invasive diagnostic tests in clinical practice.
Balance between different outcomes	The benefits of a non- or minimally invasive tests would always be preferable, but no biological markers currently exist that reliably can rule in and rule out endometriosis.
Patient values and preference	Patients are expected to prefer non- or minimally invasive tests for diagnosing endometriosis
Resource use, equity, acceptability and feasibility	Non- or minimally invasive tests (if they would be available) are considered more acceptable and feasible than invasive tests/procedures
RECOMMENDATION	**Clinicians should not use measurement of biomarkers in endometrial tissue, blood, menstrual or uterine fluids to diagnose endometriosis.**

Imaging techniques in the diagnosis of endometriosis

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
Pelvic (superficial) endometriosis							
(Nisenblat, *et al.*, 2016b)	Meta-analysis	13 studies, 1535 participants	Index test : Imaging (US) Reference test: surgical diagnosis	Diagnostic accuracy for pelvic endometriosis at all locations at any depth of invasion (sensitivity, specificity)	TVUS (5studies, n=1222) Sens = 0.65 (95% CI 0.27 to 1.00) Spec = 0.95 (95% CI 0.89 to 1.00) MRI (10 studies, n=330) Sens = 0.79 (95% CI 0.70 to 0.88) Spec = 0.72 (95% CI 0.51 to 0.90) Indirect comparisons of imaging: *See Manganaro 2012 and Thomeer 2014* Mean estimates of TVUS (after exclusion of the outlier study) showed comparable sensitivity but higher specificity than MRI. Direct comparisons of imaging: Too little data for conclusions		heterogeneous with wide confidence intervals
(Manganaro, *et al.*, 2012)	Cohort study	46 women with an ultrasound diagnosis of endometriosis and pelvic pain or infertility	Index test: 3.0TMRI Reference test : surgical diagnosis protocol: T2 weighted FRFSE HR sequences, T2 weighted FRFSE HR CUBE 3D sequences, T1w FSE sequences, LAVA-flex sequences. Pelvic anatomy, macroscopic endometriosis implants, deep endometriosis implants, fallopian tube involvement, adhesions presence, fluid effusion in Douglas pouch, uterus and kidney pathologies or anomalies associated and sacral nervous routes were considered by two radiologists in consensus.	Diagnostic accuracy for pelvic endometriosis (sensitivity, specificity)	MRI imaging diagnosed DE in 22/46 patients, endometriomas not associated to DE in 9/46 patients, 15/46 patients resulted negative for endometriosis sens = 0.97, 95%CI 0.84 to 1.00 spec = 1.00, 95% CI 0.77 to 1.00	Pelvic MRI performed with 3 T system guarantees high spatial and contrast resolution, provid-ing accurate information about endometriosis implants, with a good pre-surgery mapping of the lesions involving both bowels and bladder surface and recto-uterine ligaments.	Data as included in Nisenblat 2016

(Thomeer, *et al.*, 2014)	prospective cohort study .	40 consecutive patients with clinical suspicion of endometriosis	Index test: 3.0TMRI Reference test : surgical diagnosis Protocol: 3.0-Tesla MRI, including a T2-weighted high-resolution fast spin echo sequence (spatial resolution=0.75 x1.2 x1.5 mm(3)) and a 3D T1-weighted high-resolution gradient echo sequence (spatial resolution=0.75 x1.2 x 2.0 mm(3)). Two radiologists reviewed the dataset with consensus reading.	Diagnostic accuracy for pelvic endometriosis (sensitivity, specificity)	sens=0.81, 95%CI 0.65 to 0.92 spec=1.00, 95%CI 0.29 to 1.00 wide confidence intervals	An optimized 3.0-Tesla MRI protocol is accurate in detecting stage II to stage IV endometriosis.	Data as included in Nisenblat 2016
Ovarian endometriosis (endometrioma)							
(Nisenblat, *et al.*, 2016b)	Meta-analysis	10 studies, 852 participants	Index test : Imaging Reference test: surgical diagnosis	Diagnostic accuracy for ovarian endometriosis (sensitivity, specificity)	<u>TVUS</u> (8 studies, 765 participants) Sens = 0.93 (95%CI 0.87 to 0.99) Spec = 0.96 (95%CI 0.92 to 0.99) <u>MRI</u> (3 studies, n=179) Sens = 0.95 (95%CI 0.90 to 1.00) Spec = 0.91 (95%CI 0.86 to 0.97) <u>Indirect comparisons of imaging:</u> Most accurate US : tenderness-guided TVUS and TVUS-BP Most accurate MRI: 3.0T MRI TVUS showed lower sens but higher spec compared with MRI. <u>Direct comparisons of imaging:</u> TRUS had lower diagnostic estimates than TVUS (sensitivity 0.94, 95%CI 0.81 to 0.99; specificity 0.86, 95%CI 0.74 to 0.94) and MRI (sensitivity 0.92, 95%CI 0.78 to 0.98; specificity 0.88, 95% CI 0.76 to 0.95). TVUS and MRI provided comparable estimates for diagnosing ovarian endometriosis		
(Bazot, *et al.*, 2009).	Retrospective longitudinal study	92 consecutive patients with clinical evidence of pelvic endometriosis Clinical presentation: dysmenorrhoea 79/92, dyspareunia 63/92, dyschezia 32/92, dysuria	Index test: MRI vs TVUS vs transrectal ultrasound (TRUS) Reference test: laparoscopy 79/92 (85.9%), laparotomy 13/92 (14.1%) + histopathology	Diagnostic accuracy for ovarian endometriosis (sensitivity, specificity)	Ovarian endometriosis: Sensitivity (95% CI): 94% (81 to 99) Specificity (95% CI): 86% (74 to 94) TRUS had lower diagnostic estimates than TVUS (sensitivity 0.94, 95%CI 0.81 to 0.99;	Whilst transrectal ultrasound scan had a lower specificity and sensitivity (77% and 89%, respectively), results for transvaginal ultrasound and MRI were similarly promising.	Data as included in Nisenblat 2016

		3/92, infertility 21/92; history of surgery for endometriosis 31/92 Age: median 31.8 years (range 20 - 50 years)			specificity 0.86, 95%CI 0.74 to 0.94) and MRI (sensitivity 0.92, 95%CI 0.78 to 0.98; specificity 0.88, 95% CI 0.76 to 0.95). TVUS and MRI provided comparable estimates for diagnosing ovarian endometriosis		
Deep endometriosis							
(Nisenblat, *et al.*, 2016b)	Meta-analysis	15 studies, 1493 participants	Index test : Imaging Reference test: surgical diagnosis	Diagnostic accuracy for DIE/posterior DE (sensitivity, specificity)	<u>TVUS</u> (9 studies, n=934) Sens = 0.79 (95%CI 0.69 to 0.89) Spec = 0.94 (95%CI 0.88 to 1.00) <u>MRI</u> (6 studies, n=266) Sens = 0.94 (95% CI 0.90 to 0.97) Spec = 0.77 (95% CI 0.44 to 1.00) <u>Indirect comparisons of imaging:</u> Most accurate US: TVUS-BP (1 study) Most accurate MRI: 3.0TMRI (2 studies) and MRI jelly method (1 study) <u>Direct comparisons of imaging:</u> tenderness-guided TVUS vs 3D-TVUS see *Guerriero 2007 and 2014* TVUS had lower estimates of sens and spec compared with SVG (1study, n=46) 3D-MRI had higher sensitivity than 2D-MRI (1 study, n=23) MRI appeared to be superior to 3D-TVUS (1 study, n=58)		
(Guerriero, *et al.*, 2014)	Prospective study	202 patients scheduled for surgery because of clinical suspicion of deep pelvic endometriosis	Index test : 2D US versus 3D US Reference test: laparoscopy	Diagnostic accuracy (sensitivity, specificity)	<u>conventional TVUS</u> sens = 0.71, 95% CI 0.61 to 0.80; spec = 0.88, 95% CI 0.81 to 0.94 <u>3D-TVUS</u> Sens = 0.87, 95% CI 0.78 to 0.93 Spec = 0.94, 95% CI 0.87 to 0.97) conventional TVUS is less accurate than 3D-TVUS	3D US has a significantly higher diagnostic accuracy in the diagnosis of posterior locations of DE without intestinal involvement, such as the uterosacral ligaments, vaginal and rectovaginal endometriosis.	Data as included in Nisenblat 2016
(Bazot, *et al.*, 2009)	Retrospective longitudinal study	92 consecutive patients with clinical evidence of pelvic endometriosis	Index test: MRI vs TVUS vs transrectal ultrasound (TRUS)	Diagnostic accuracy (sensitivity, specificity)	<u>TRUS</u> RES / Sensitivity / Specificity USLs 48.2% (40/83) 44.4% (4/9) Vagina 6.7% (2/30) 100% (62/62) RV septum 18.2% (2/11) 95% (77/81) Intestine 88.9% (56/63) 93.1% (27/29)	MRI is the best imaging technique for mapping DIE	Data as included in Nisenblat 2016

		Clinical presentation: dysmenorrhoea 79/92, dyspareunia 63/92, dyschezia 32/92, dysuria 3/92, infertility 21/92; history of surgery for endometriosis 31/92 Age: median 31.8 years (range 20 - 50 years)	Reference test: laparoscopy 79/92 (85.9%), laparotomy 13/92 (14.1%) + histopathology		TVUS TVS / Sensitivity / Specificity USLs 78.3% (65/83) 66.7% (6/9) Vagina 46.7% (14/30) 95% (59/62) RV septum 9% (1/11) 98.7% (80/81) Intestine 93.6% (59/63) 100% (29/29) MRI MRI / Sensitivity / Specificity USLs 84.4% (70/83) 88.9% (8/9) Vagina 80% (24/30) 85.5% (53/62) RV septum 54.5% (6/11) 98.7% (80/81) Intestine 87.3% (55/63) 93.1% (27/29)		
Deep endometriosis Rectosigmoid							
(Moura, *et al.*, 2019)	Systematic review	8 studies (n = 1132)	Index test: MRI / TVUS Reference test: laparoscopy	Diagnostic accuracy for Deep endometriosis Rectosigmoid (sensitivity, specificity)	MRI Sens = 90% (87 – 92%) Spec = 96% (94 - 97%) TVUS sens = 90% (87 – 92%) spec = 96% (94 - 97%) Areas under the S-ROC curves (AUC) showed no statistically significant differences between MRI (AUC = 0.948) and TVS (AUC = 0.930) in the diagnosis of RE (P = 0.13).	MRI and TVS have similarly high accuracy and positive post-test probabilities in the noninvasive diagnosis of RE.	

INCLUDED AS BACKGROUND INFORMATION
(Wykes, *et al.*, 2004)

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	Observational data of diagnostic accuracy are summarized in systematic reviews and meta-analysis. These confirm good diagnostic accuracy of imaging for detection of endometrioma and deep endometriosis, but not for superficial lesions. Quality of evidence: ⊕⊕◯◯ (based on high/unclear risk of bias of the studies included in the reviews and the heterogeneity among studies)
Balance between desirable and undesirable outcomes	The desirable outcomes (i.e. accurate diagnosis) should be balanced against the need for diagnostic laparoscopy and consequences of that. It was considered that diagnostic confirmation via imaging prevents the need for diagnostic laparoscopy. This resulted in a strong recommendation. Limited sensitivity for superficial disease may lead to false negative results, with significant implications for delay of care/treatment for the patients. The latter is addressed in a GPP
Balance between different outcomes	Emphasis was placed on time to diagnosis through accessibility of imaging.

	Another important outcome is diagnostic accuracy, and therefore, the limitations of imaging are highlighted in the rec and GPPs
Patient values and preference	Imaging techniques are well tolerated by adult patients. Specific considerations in adolescents are covered in the respective chapter
Resource use, equity, acceptability and feasibility	(Some type of) Imaging is likely to be available and imaging studies are considered feasible.
RECOMMENDATION	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.
GPP	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.

QUESTION I.5 DOES DIAGNOSTIC LAPAROSCOPY COMPARED TO EMPIRICAL MEDICAL TREATMENT RESULT IN BETTER SYMPTOM MANAGEMENT IN WOMEN SUSPECTED OF ENDOMETRIOSIS?

Summary of Findings Table

Not applicable

EVIDENCE TABLE

We found no studies comparing diagnostic laparoscopy and empirical medical treatment and their impact on (pain) symptoms. The evidence tables includes indirect evidence, focussing on the risks of surgery in endometriosis.

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Bafort, *et al.*, 2020a)	SR	4 RCTs compared laparoscopic ablation or excision with diagnostic laparoscopy only (Gad 2012; Marcoux 1997; Moini 2012; Tutunaru 2006). two RCTs compared laparoscopic excision with diagnostic laparoscopy only (Abbott 2004; Jarrell 2005).	laparoscopic intervention versus diagnostic laparoscopy.	Overall pain (Live birth)		Compared to diagnostic laparoscopy only, it is uncertain whether laparoscopic surgery reduces overall pain associated with minimal to severe endometriosis.	
(Byrne, *et al.*, 2018b)	multicentre, prospective cohort study	5162 women of reproductive age with rectovaginal endometriosis of which 4721 women had planned laparoscopic excision	Laparoscopic surgical excision of rectovaginal endometriosis requiring dissection of the pararectal space.	Standardised symptom questionnaires (chronic pelvic pain, bladder and bowel symptoms, analgesia use and quality of life) completed prior to surgery and at 6, 12 and 24 months postop. Serious perioperative and postoperative complications including major haemorrhage, infection and visceral injury were recorded	At 6 months postop, there were significant reductions in premenstrual, menstrual and non-cyclical PP, deep dyspareunia, dyschezia, low back pain and bladder pain, voiding difficulty, bowel frequency, urgency, incomplete emptying, constipation and passing blood. These reductions were maintained at 2 years, with the exception of voiding difficulty. Global quality of life significantly improved from a median pretreatment 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.	Laparoscopic surgical excision of rectovaginal endometriosis appears to be effective in treating pelvic pain and bowel symptoms and improving health-related quality of life and has a low rate of major complications when performed in specialist centres.	

					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). GI 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.		
(Chapron, *et al.*, 1998)	multicentre cohort study	29 966 surgeries	diagnostic and operative laparoscopic operations diagnostic laparoscopy (19.9%; n=5983), minor laparoscopic surgery (19.8%; n=5922), major laparoscopic surgery (48.8%; n=14 622) and advanced laparoscopic surgery (11.5%; n=3439). Over half the operations (60.3%; n=18 061) were major or advanced laparoscopic surgery.	risk of complications	Mortality rate: 3.33 per 100 000 laparoscopies Overall complication rate was 4.64 per 1000 laparoscopies (n=139) The complication rate was related to the level of sophistication of the surgical procedure.		

INCLUDED AS BACKGROUND INFORMATION
(Kennedy, *et al.*, 2005, Kuznetsov, *et al.*, 2017, Zondervan, *et al.*, 2020)

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	There are no studies specifically investigating whether diagnostic laparoscopy and further endometriosis treatment is better compared to (imaging +) empirical medical treatment for suspected endometriosis. One consideration could be possible risks of surgery, and studies on risk of laparoscopy were listed.
Balance between desirable and undesirable outcomes	There is no evidence of superiority of either approach for any outcome. The psychosocial benefit of a confirmed diagnosis for an individual patient should be weight against the value and risks of laparoscopic surgery.
Balance between different outcomes	NA
Patient values and preference	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.

Resource use, equity, acceptability and feasibility	Laparoscopic surgery, albeit its widespread use, is expensive, invasive, and associated with morbidity and mortality Empirical treatment without confirmed diagnosis is widely applied
RECOMMENDATION	Based on the lack of direct evidence, the GDG decided to formulate the following statement: Both diagnostic laparoscopy and imaging combined with empirical treatment (oral contraceptive pill 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.

QUESTION I.6 IS LONG TERM MONITORING OF WOMEN WITH ENDOMETRIOSIS BENEFICIAL IN PREVENTING ADVERSE OUTCOMES (RECURRENCE, COMPLICATIONS, MALIGNANCY) ?

Summary of Findings Table

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

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Pittaway, 1990)	Cohort study	134 consecutive infertile women with endometriosis. 76 (57%) women had pre-op CA-125 values greater than or equal to 16 U/ml and were followed up for 18 months.	serial determinations of CA 125 concentrations	Correlation with surgical findings Relevance to estimate (fertility) prognosis	Changes in the CA 125 values correlated with the surgical findings in 24 of the 26 women (92%) who had a second-look operative procedure. At the 6-, 12-, and 18-month intervals, pregnancies occurred in 18 of 45 (30%), 14 of 24 (58%), and 5 of 12 (42%) women in the good prognosis group, respectively; pregnancy rates in the poor prognosis group were 1 of 31 (3%), 2 of 33 (6%), and 0 of 26 (0%) women (p less than 0.001).	The study supports the use of serial CA 125 concentrations to assist in the management of women with endometriosis.	Very low quality evidence
(Matalliotakis, *et al.*, 1994)	Cohort study	endometriotic women versus normal controls 40 women, aged 21 to 33 years	CA-125 levels In patients, before treatment, during the last 15 days of a 6-month administration of Danazol, and 3 months after treatment In controls, 1 sample	Monitoring the effect of treatment (disease progression)	CA-125 levels were significantly higher in patients with endometriosis before treatment as compared with the controls (P < .01). The administration of Danazol significantly reduced the levels of CA-125 (P < .01), and 3 months after treatment the levels of CA-125 remained significantly lower (P < .05) as compared to the respective pretreatment values.	CA-125 levels may assist in (a) evaluating women with endometriosis and (b) treatment with Danazol.	Very low quality evidence
(Chen, *et al.*, 1998)	Cohort study	Women with endometriosis under danazol treatment after conservative surgery	CA-125 Elevated CA-125 = CA-125 >35 U/ml	CA-125 for monitoring the effect of treatment and recurrence (data on CA-125 for diagnosis are not reported here)	Elevated CA-125 in 65/75 cases (86.70%) with advanced endometriosis, but in only 15/56 patients (26.8%) with minimal and mild endometriosis. 10 advanced endometriosis were found with persistent endometriosis by laparoscopy during danazol treatment, even	For endometriosis, CA-125 is a valuable adjuvant in the follow-up of recurrence in patients with advanced endometriosis and initially elevated CA-125 levels. It is not an effective screening tool for patients with dysmenorrhea, or for monitoring therapy. There	Very low quality evidence

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
					though they tested with normal CA-125 levels (<35 U/ml) at that time. 15 patients had elevated CA-125 levels before and one year after therapy, and were confirmed with recurrence of endometriosis by laparoscopy. 9 women with elevated CA-125 levels before treatment, were found without recurrence of endometriosis and had normal CA-125 levels one year after therapy.	was no significant correlation between the development of endometriosis and reproductive factors.	

INCLUDED AS BACKGROUND INFORMATION
(Evers, 2013, Guo, 2009)

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	There currently exist no studies of sufficient quality or size to address the question of whether patients with endometriosis should be monitored long term. Evidence (very low quality) could be collected for CA-125 as monitoring tool, while no evidence was found with regards to the relevance of monitoring through ultrasound/imaging. Quality of evidence: ⊕◯◯◯
Balance between desirable and undesirable outcomes	The desirable outcomes linked to monitoring are early detection of recurrence, complications, malignancy with an earlier start of appropriate management, which may be less complex and reduced risk of symptom development. The undesirable outcomes include unnecessary extra invasive procedures and treatment side effects.
Balance between different outcomes	Overall, the benefits of monitoring would outweigh the harms, especially in patients with possible future complications (endometrioma/DE) and it was recommended that monitoring should be considered (specifically in this patient population)
Patient values and preference	No information on patient preferences
Resource use, equity, acceptability and feasibility	The feasibility of (imaging) monitoring for peritoneal disease is questionable.

	Also, the costs and feasibility of monitoring in general were considered the basis for the GPP, which allows targeting monitoring/follow-up to specific individual patients, and allowing flexibility in monitoring to ensure feasibility.
RECOMMENDATION	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.
GPP	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.

QUESTION I.7 DOES EARLY DIAGNOSIS OF ENDOMETRIOSIS VERSUS LATE DIAGNOSIS LEAD TO BETTER QUALITY OF LIFE?

NARRATIVE QUESTION

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Not applicable

INCLUDED REFERENCES FOR NARRATIVE DISCUSSION
(Ballard*, et al.*, 2006, Culley*, et al.*, 2013a, Culley*, et al.*, 2013b, Jones*, et al.*, 2004, Jones*, et al.*, 2001).

EVIDENCE TO RECOMMENDATIONS

Not applicable

The GDG formulated the following 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.

This statement is based on the following considerations:

- To date, there is insufficient direct evidence that either early or late diagnosis of endometriosis leads to a difference in quality of life.
- Reports have suggested that early diagnosis may be of benefit individuals suffering at physical, emotional and social levels.
- The benefits of early diagnosis include early focused treatment, reassurance for affected individuals, and avoidance of potential emotional, physical and social side effects. The risks could include the need for additional procedures and distress from receiving a diagnosis.
- Affected individuals often want to have a diagnosis
- There is no information on the (societal/patient) costs of early versus late endometriosis diagnosis

QUESTION II.1 ARE ANALGESICS EFFECTIVE FOR SYMPTOMATIC RELIEF OF PAINFUL SYMPTOMS ASSOCIATED WITH ENDOMETRIOSIS ?

NSAIDS

Summary of findings

II.1a NSAIDs compared to placebo for symptomatic relief of painful symptoms associated with endometriosis

Patient or population: symptomatic relief of painful symptoms associated with endometriosis
Setting:
Intervention: NSAIDs
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with NSAIDs				
Overall pain relief follow up: median 2 months	50 per 100	**77 per 100** (38 to 95)	**OR 3.27** (0.61 to 17.69)	24 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Downgraded one level owing to overall unclear risk of bias for included trial.
b. Downgraded two levels for imprecision because confidence interval is wide, consistent with benefit and harm and evidence based on a single small trial.

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Kauppila and Ronnberg, 1985)	RCT	See SOF table 2.1					
(Brown, *et al.*, 2017)	Cochrane review	See SOF table 2.1					

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	Very low quality evidence of benefit (or any evidence at all due to paucity of studies) for all analgesics - unchanged from 2013 version of guideline New meta-analyses of NSAIDS treatments for endometriosis (Cochrane Database Syst Rev 2017;1: Cd004753) – low quality evidence This review includes two trials, but they included only one trial (naproxen), with 24 women, in the analysis. No evidence shows whether any individual NSAID is more effective than another. As shown in the Cochrane review, women taking NSAIDs must be aware that these drugs may cause unintended effects. Quality of evidence : ⊕◯◯◯
Balance between desirable and undesirable outcomes	Benefit: general anti-inflammatory effect of some analgesics; potential use in conjunction with surgery and/or hormonal treatments; possible prevention of complications of chronic pain (e.g. peripheral and central sensitisation) Risks: limited side effects of most analgesics but note potential gastrointestinal effects of NSAIDs
Balance between different outcomes	Generally limited risks. No evidence that analgesics have a negative effect on disease progression.
Patient values and preference	Shared decision-making approach recommended
Resource use, equity, acceptability and feasibility	Consider costs of each approach and availability (different across countries).
RECOMMENDATION	**Women may be offered NSAIDs or other analgesics (either alone or in combination with other treatments) to reduce endometriosis-associated pain.**

Anti-TNF alpha

Summary of findings:

II.1b Anti-TNF alpha compared to placebo for relief of pelvic pain

Patient or population: relief of pelvic pain
Setting:
Intervention: anti-TNF alpha
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with anti-TNF alpha				
VAS SCORE	The mean VAS SCORE was **50.14**	MD **5.6 lower** (16.1 lower to 4.9 higher)	-	21 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	

Explanations

a. Downgraded one level owing to overall unclear risk of bias for included trial.
b. Downgraded two levels for imprecision because confidence interval is wide, consistent with benefit and harm and evidence based on a single small trial

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Koninckx, *et al.*, 2008)	RCT	See SOF table 2.2					
(Lu, *et al.*, 2013)	Cochrane review	See SOF table 2.2					

INCLUDED AS BACKGROUND INFORMATION
(Horne, *et al.*, 2020, Norman, 2001)

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	anti-TNF-α** treatments for endometriosis (Cochrane Database Syst Rev 2013: Cd008088) – low quality evidence Quality of evidence : ⨁◯◯◯

Balance between desirable and undesirable outcomes	Same as above
Balance between different outcomes	Same as above
Patient values and preference	Same as above
Resource use, equity, acceptability and feasibility	Same as above
RECOMMENDATION	NO RECOMMENDATION WAS FORMULATED, as the evidence includes only a single small trial. The evidence is considered insufficient to recommend the use of anti-TNF-α drugs in the clinical management of women with endometriosis.

QUESTION II.2 ARE HORMONE THERAPIES EFFECTIVE FOR PAINFUL SYMPTOMS ASSOCIATED WITH ENDOMETRIOSIS?

Medical treatments

Summary of Findings Table / EVIDENCE TABLES

Evidence for the individual medical/hormone treatments is listed below per treatment.

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	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). Quality of evidence: ⊕⊕⊕◯
Balance between desirable and undesirable outcomes	Efficacy is weight against safety and availability. There is no evidence of superiority of one hormone treatment compared to others Considering other options are available (surgical treatment) and there is a lack of evidence on superiority, the recommendation was phrases as “one of the options for treatment”
Balance between different outcomes	Efficacy seems to overrule safety issues and side effects. Still, individual patients may experience significant side effects requiring discontinuation of the treatment. The balance between efficacy and side effects needs to be considered at an individual patient level, and a GPP on shared decision-making was added to the recommendation
Patient values and preference	No data. Hormone treatments, such as the contraceptive pill, may be indicated for contraception anyway.
Resource use, equity, acceptability and feasibility	The costs and availability vary between the different interventions and between different countries/regions. No conclusion can be drawn, and it was suggested to consider costs and availability in shared decision making.
RECOMMENDATION	**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.**
GPP	**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.**

Combined Hormonal contraceptives– efficacy (compared to no treatment/other treatment)

Summary of Findings Table

II.2a OCP compared to no treatment for endometriosis-associated pain

Patient or population: endometriosis-associated pain
Setting:
Intervention: OCP
Comparison: no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no treatment	Risk with OCP				
Self- reported pain: menstrual pain reduction from baseline to end of treatment (VAS)	The mean self- reported pain: menstrual pain reduction from baseline to end of treatment (VAS) was **3.00**	MD **2.1 lower** (1.38 lower to 2.82 lower)	-	169 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	based on Brown 2018 (RCT Harada 2017)
Self- reported pain (dysmenorrhoea) at the end of treatment: dysmenorrhoea VAS	The mean self- reported pain (dysmenorrhoea) at the end of treatment: dysmenorrhoea VAS was **46.2**	MD **23.68 lower** (28.75 lower to 18.62 lower)	-	327 (2 RCTs)	⊕⊕◯◯ LOW [a]	based on Brown 2018 (RCT Harada 2008, 2017)
Reduction in severest dyspareunia from baseline to end of treatment	The mean reduction in severest dyspareunia from baseline to end of treatment was **0.1 (2.1)**	MD **1.4 lower** (0.46 lower to 2.34 lower)	-	89 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	based on Brown 2018 (RCT Harada 2017)
Reduction in non-menstrual pain from baseline to end of treatment	The mean reduction in non-menstrual pain from baseline to end of treatment was **0.4 (SD 2.6)**	MD **1 higher** (0.3 higher to 1.7 higher)	-	212 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	based on Brown 2018 (RCT Harada 2017) [a]

Explanations
a. trial judged to be at high risk of bias; downgraded two levels.
b. evidence was based on a single small trial; downgraded one level.
c. Imprecision detected

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Grandi, *et al.*, 2019)	Systematic review	Women with endometriosis	Hormonal contraceptive therapies (combined hormonal contraceptives [CHCs], combined oral contraceptives [COCs] *progestin-only pills [POPs] and progestin-only contraceptives [POCs])*	endometriosis-related pain (dysmenorrhoea, pelvic pain and dyspareunia), quality of life (QoL) and postoperative rate of disease recurrence during treatment	CHC and POC treatments were associated with clinically significant reductions in dysmenorrhoea, often accompanied by reductions in non-cyclical pelvic pain and dyspareunia and an improvement in QoL. Only two COC preparations (ethinylestradiol [EE]/norethisterone acetate [NETA] and a flexible EE/drospirenone regimen) demonstrated significantly increased efficacy compared with placebo.	CHCs and POCs are effective for the relief of endometriosis-related dysmenorrhoea, pelvic pain and dyspareunia, and improve QoL. There is insufficient evidence to reach definitive conclusions about the overall superiority of any particular hormonal contraceptive.	No meta-analysis performed
(Jensen, *et al.*, 2018)	Systematic review	Women with endometriosis 9 RCTs and 9 observational studies	Combined hormonal contraceptive agents, active comparators, placebo, or no treatment.	Endometriosis-related pain (dysmenorrhea, pelvic pain, and dyspareunia).	CHC treatment, administered cyclically or continuously, results in clinically important and statistically significant reductions from baseline in endometriosis-related pain. dysmenorrhea (100-mm VAS scores) : clinically significant reductions in all studies noncyclic pelvic pain and dyspareunia: clinically significant reductions in all studies QoL :improvements from baseline in most studies		No meta-analysis performed
(Brown, *et al.*, 2018)	Systematic review	Women with endometriosis	Combined hormonal contraceptive agents versus Placebo – no treatment				SEE SOF TABLE
		Women with endometriosis 1 RCT - 50 women (Vercellini, *et al.*, 1993)	Combined hormonal contraceptive agents versus Goserelin	Dysmenorrhoea non-menstrual pain no clear evidence of a difference betweenthe COCP and goserelin groups for reporting	At 6 mo FU – goserlin vs OCP: dysmenorrhoea • VAS scale (scale 1 to 10) (MD -0.10, 95% CI -1.28 to 1.08) • verbal rating scale 0 to 3 (MD -0.10, 95% CI -0.99 to 0.79). complete absence of pain • VAS (risk ratio (RR) 0.36, 95%CI 0.02 to 8.43) • VRS (RR 1.00, 95%CI 0.93 to 1.08).	no clear evidence of a difference between women treated with the COCP and women treated with goserelin	

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	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). The conclusions are based on systematic reviews that reported factors to be considered in the quality of evidence, including a low number of RCTs per outcome, small number of participants, heterogeneity in the reported outcomes and comparators. Quality of evidence: ⊕⊕◯◯
Balance between desirable and undesirable outcomes	Efficacy is weight against safety and availability.
Balance between different outcomes	OCP is considered a safe treatment and efficacy overrule any safety concerns.
Patient values and preference	No data.
Resource use, equity, acceptability and feasibility	OCP is cost-effective (cheap), considered safe and often required for contraception. OCP is acceptable and feasible
RECOMMENDATION	**It is recommended to prescribe individuals a combined hormonal contraceptive to reduce endometriosis-associated dyspareunia, dysmenorrhea and non-menstrual pain.**

Combined Hormonal contraceptives – Continuous vs cyclic use

Summary of Findings Table

II.2b OCP (continuous use) compared to OCP (cyclic use) for endometriosis-associated pain

Patient or population: endometriosis-associated pain
Intervention: OCP (continuous use)
Comparison: OCP (cyclic use)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with OCP (cyclic use)	Risk with OCP (continuous use)				
Dysmenorrhea recurrence follow up: 6 months	237 per 1,000	**57 per 1,000** (14 to 216)	**RR 0.24** (0.06 to 0.91)	496 (2 RCTs + 1 observational study)	⨁◯◯◯ VERY LOW [a,b,c]	Based on Muzii 2016
Chronic pelvic pain recurrence follow up: 6 months	317 per 1,000	**193 per 1,000** (114 to 327)	**RR 0.61** (0.36 to 1.03)	496 (2 RCTs + 1 observational study)	⨁◯◯◯ VERY LOW [a,b,d]	Based on Muzii 2016
Dyspareunia recurrence follow up: 6 months	224 per 1,000	**172 per 1,000** (116 to 251)	**RR 0.77** (0.52 to 1.12)	439 (1 RCT + 1 observational study)	⨁◯◯◯ VERY LOW [b,d]	Based on Muzii 2016
Safety - Effect on coagulation			No difference	(1 RCT + 1 case-control)	⨁◯◯◯ VERY LOW [a,e,f]	Based on Hee, 2013
Safety - Effect on hemostatic parameters, lipids and carbohydrate metabolism			No difference in the lipid profiles	4 RCTs	⨁◯◯◯ VERY LOW [e,f]	Based on Hee, 2013
		Increase in total cholesterol, HDL, triglycerides and VLDL		1 RCT		
			No difference in hemostatic parameters	3 RCTs		
			No difference in fasting glucose or insulin level	2 RCTs		
Safety - risk of VTE or arterial complications				no comparative studies	na	Based on Hee, 2013
Safety - Effect on bone metabolism and bone mineral density	no significant effect	no significant effect	No difference	144 (2 RCTs)	⨁◯◯◯ VERY LOW [e,f]	Based on Hee, 2013

Explanations
a. Combination of RCT and prospective study

b. Post-operative use of OCP
c. Small studies with large confidence intervals
d. Imprecision detected
e. Indirect evidence (not endometriosis specific)
f. Unclear whether studies were powered to detect differences in safety profiles

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Muzii, *et al.*, 2016b)	systematic review (4 studies: Muzii 2011, Seracchioli 2010 + 2010, Vlahos 2013)	Endometriosis patients after surgical intervention	OCP continuous (CON) versus cyclic use (CY)	Dysmenorrhea recurrence Chronic pelvic pain recurrence Dyspareunia recurrence follow up at least 6 months in all studies	SEE SOF TABLE		
(Zorbas, *et al.*, 2015)	systematic review (4 studies: Vercellini 2003, Seracchioli 2010 + 2010, Vlahos 2013) Vercellini 2003 had no control group	Endometriosis patients after surgical intervention	OCP continuous (CON) versus cyclic use (CY)	Dysmenorrhea (24mo) (3 studies, incl vercellini 2003) Dyspareunia (2 studies) non-menstrual pelvic pain (2 studies)	2 studies: - Recurrence of dysm: 30% in CY group, 4% in CON group - Recurrence of dysm: 20.9% in CY group, 9.4% in CON group		Meta-analysis not possible Data are indirect evidence, as postoperative use of OCP
(Hee, *et al.*, 2013)	systematic review (section safety)	Not endometriosis specific (safety data)	OCP continuous (CON) versus cyclic use (CY)	Safety Effect on coagulation Effect on Hemostatic parameters, lipids and carbohydrate metabolism risk of VTE or arterial complications Effect on bone metabolism and bone mineral density	SEE SOF TABLE No increase in hemoglobin concentration (1 RCT + 1 case-control) No significant difference in the lipid profiles (4 RCTs) Increase in total cholesterol, HDL, triglycerides and VLDL (1 RCT) hemostatic parameters similar (3 RCTs) No difference in fasting glucose or insulin level (2 RCTs) no comparative studies (CY vs CON) no significant effect on bone metabolism and BMD (2 RCTs)		

INCLUDED AS BACKGROUND INFORMATION
(Vercellini, *et al.*, 2003b)

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	Studies consistently show no negative effect of continuous use of the OCP compared to cyclical use (at least for post-operative use). A review by Hee *et al* reported no difference in the safety profile of both regimens (Hee*, et al.*, 2013)(indirect data from non-endometriosis). The data for efficacy are deduced from few small studies, although summarized in a meta-analysis. Quality of evidence: ⊕⊕○○ Hypothesis: continuous treatment may homogenize the hormonal milieu and increase the efficiency of therapy
Balance between desirable and undesirable outcomes	No difference in safety or efficacy.
Balance between different outcomes	Not relevant as there is no difference in safety or efficacy
Patient values and preference	Patients with endometriosis may prefer a regimen that induces amenorrhea
Resource use, equity, acceptability and feasibility	Continuous use is acceptable and feasible
RECOMMENDATION	**Women suffering from endometriosis-associated dysmenorrhea can be offered the continuous use of a combined hormonal contraceptive pill.**

Combined Hormonal contraceptives – vaginal contraceptive ring versus transdermal (estrogen/progestagen) patch

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Grandi, *et al.*, 2019)	Systematic review	Women with endometriosis	contraceptive ring vs patch (sub-analysis)	endometriosis-related pain, quality of life (QoL) and disease recurrence during treatment	2 trails included (Leone Roberti Maggiore, *et al.*, 2014, Vercellini, *et al.*, 2010a), but no meta-analysis performed		No meta-analysis performed
(Vercellini, *et al.*, 2010a)	Patient preference prospective cohort study	206 patients: 123 preferred 12 month treatment with vaginal ring vs 84 transdermal patch	The study compared compared two estrogen-progestogen combinations delivered by two different systems, a vaginal ring and a transdermal patch, for the treatment of recurrent pelvic pain after conservative surgery for symptomatic endometriosis	**Primary endpoint:** Satisfaction rate. **Secondary outcomes:** pain symptoms reduction (presence and severity)	36/79 subjects (46%) in the ring group and 14/33 (42%) in the patch group shifted from continuous to cyclic use because of irregular bleeding. Pain symptoms were reduced by both treatments, with the ring being more effective than the patch in patients with rectovaginal lesions. According to an intention-to-treat analysis, 88 of 123 ring users (72%) and 40 of 84 patch users (48%) were satisfied with the treatment received.	Patients who preferred the ring were significantly more likely to be satisfied and to comply with treatment than those who chose the patch. Both systems were associated with poor bleeding control when used continuously	
(Leone Roberti Maggiore, *et al.*, 2014)	patient preference prospective study	143 women of reproductive age with rectovaginal endometriotic nodules infiltrating the rectum	continuous oral treatment with desogestrel 75 µg/day or combined sequential contraceptive vaginal ring [15 µg ethinylestradiol and 120 µg etonogestrel; through days 1–21 of the menstrual cycle Choice of the treatment : preference of the patient. Duration of treatment: 12 months	presence and severity of dysmenorrhea, deep dyspareunia, non-menstrual pelvic pain and dyschezia (evaluated by 10-cm VAS) Assessment: - Before starting, - at 6 months - at12 months	In desogestrel group: - symptoms associated with menstruation disappeared during treatment. - At 12-month FU; significant amelioration in the intensity of all pain and gastrointestinal symptoms (except abdominal bloating) compared with baseline In the ring group: - At 12-month follow up, significant amelioration in the severity of all pain and gastrointestinal symptoms (except diarrhea during menstruation and passage of mucus) Group comparison: - At 12-month FU, the intensity of CPP, dyschezia, deep dyspareunia, diarrhea, intestinal cramping, feeling of incomplete evacuation and	this study confirms that hormonal therapies are effective in the management of bowel endometriosis related symptoms. The rate of satisfaction with treatment was higher in patients treated with desogestrel than in those treated with the vaginal ring; however, the rate of dissatisfied patients was similar in both study groups (about 22%). Both pain and gastrointestinal symptoms (such as diarrhea and intestinal cramping) improved more in group D	

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
					passage of mucus was significantly lower in group D. No significant difference in the intensity of constipation and abdominal bloating		

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	Both ring and patch are effective for treating endometriosis associated pain. Evidence is based on 2 patient preference studies, there are no RCTs comparing the 2 interventions.
Balance between desirable and undesirable outcomes	Studies focussed on patient preference and symptom reduction. Safety aspects or side effects were not reported.
Balance between different outcomes	Not relevant
Patient values and preference	Patients seemed to be satisfied with both patch and ring
Resource use, equity, acceptability and feasibility	There is no evidence on resource use, equity, acceptability and feasibility
RECOMMENDATION	*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.* *It was specified in recommendation 13 that combined hormonal contraceptives includes oral, vaginal ring or transdermal adminstration.*

Progestogens

Summary of Findings Table

II.2c Progestogens compared to no treatment for endometriosis-associated pain

Patient or population: endometriosis-associated pain
Intervention: progestagens
Comparison: no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no treatment	Risk with progestogens				
Patient assessed efficacy, sum of all symptoms follow up: mean 6 months	The mean patient assessed efficacy, sum of all symptoms was **-5.20**	**5.2 lower** (6.8 lower to 3.6 lower)	-	33 (1 RCT)	⨁⨁◯◯ LOW [a,b]	Based on Brown 2012 - RCT Telimaa 1987
Patient assessed efficacy, sum of all symptoms follow up: mean 12 months	The mean patient assessed efficacy, sum of all symptoms was **-7.0**	**7 lower** (8.61 lower to 5.39 lower)	-	29 (1 RCT)	⨁⨁◯◯ LOW [a,b]	Based on Brown 2012 - RCT Telimaa 1987
Pain follow up: 6 months	The mean pain was **41.8 (SD 28.6)**	MD **1.6 lower** (9.1 lower to 5.9 higher)	-	252 (1 RCT)	⨁⨁◯◯ LOW [b,c]	Based on Brown 2012 - RCT Strowitzki 2010
Pain follow up: 6 months	The mean pain was **0.4 (SD 0.55)**	MD **0.1 higher** (0.26 lower to 0.46 higher)	-	34 (1 RCT)	⨁⨁◯◯ LOW [a,b]	Based on Brown 2012 - RCT Telimaa 1987

Explanations
a. There was an unclear explanation for randomisation, allocation concealment and blinding
b. Evidence based on a single trial
c. Wide confidence interval indicating imprecision

II.2d Progestagens compared to other treatment for endometriosis-associated pain

Patient or population: endometriosis-associated pain
Intervention: progestagens
Comparison: other treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with other treatment	Risk with progestagens				
Dysmenorrhea follow up: 6 months	978 per 1,000	**895 per 1,000** (692 to 969)	**OR 0.19** (0.05 to 0.69)	274 (1 RCT)	⨁⨁◯◯ LOW [a]	Based on Brown 2012 - RCT Schlaff 2006
Dysmenorrhea follow up: 12 months	768 per 1,000	**676 per 1,000** (551 to 782)	**OR 0.63** (0.37 to 1.08)	274 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	Based on Brown 2012 - RCT Schlaff 2006
Dyspareunia follow up: 6 months	848 per 1,000	**786 per 1,000** (667 to 873)	**OR 0.66** (0.36 to 1.23)	274 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	Based on Brown 2012 - RCT Schlaff 2006
Dyspareunia follow up: 12 months	768 per 1,000	**941 per 1,000** (876 to 973)	**OR 4.83** (2.14 to 10.93)	274 (1 RCT)	⨁⨁◯◯ LOW [a]	Based on Brown 2012 - RCT Schlaff 2006
Pelvic pain follow up: 6 months	862 per 1,000	**830 per 1,000** (720 to 905)	**OR 0.78** (0.41 to 1.52)	274 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	Based on Brown 2012 - RCT Schlaff 2006
Pelvic pain follow up: 12 months	812 per 1,000	**802 per 1,000** (687 to 880)	**OR 0.94** (0.51 to 1.71)	274 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	Based on Brown 2012 - RCT Schlaff 2006
Patient assessed efficacy - pain follow up: mean 6 months	The mean patient assessed efficacy - pain was **21.1**	**0.1 higher** (0.26 lower to 0.46 higher)	-	286 (2 RCTs)	⨁⨁◯◯ LOW [c]	Based on Brown 2012

Explanations

a. Evidence based on a single trial

b. Wide confidence intervals indicative of imprecision

c. One trial did not provide adequate explanation for randomisation, allocation concealment or blinding and the other trial was open label

II.2e Anti-progestagens compared to other treatment for endometriosis-associated pain

Patient or population: endometriosis-associated pain
Intervention: Anti-progestagens
Comparison: other treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with other treatment	Risk with anti-progestagens				
Patient assessed efficacy none or mild dysmenorrhoea follow up: 6 months	667 per 1,000	**673 per 1,000** (524 to 794)	**OR 1.03** (0.55 to 1.93)	266 (2 RCTs)	⨁⨁◯◯ LOW [a]	

Explanations

a. Inadequate explanation of randomisation and allocation concealment, one of the trials was open label

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Brown, *et al.*, 2012)	Systematic review	Endometriosis	depot MPA, cytoproterone acetate, MPA, desogestrel and dienogest. Gestrinone versus no treatment/placebo Versus other treatment		Progestagens versus no treatment/placebo **SEE SOF TABLE A** Progestagens versus other treatment **SEE SOF TABLE B** Anti progestagens versus other treatment **SEE SOF TABLE C**		
(Andres Mde, *et al.*, 2015)	Systematic review	Endometriosis	Dienogest versus placebo (1 RCT – Strowitzki 2010)		Both DNG and placebo reduced the painful symptoms (VAS) - DNG presented superior results (27.4 versus 15.1 mm) side effects : headache (10.8 % DNG versus 5.2 % placebo), nausea (2.9versus 1.0) and cystitis (2.9 versus 0).		Includes the same studies as Brown 2012 SEE SOF TABLE A
	Systematic review - (Petraglia 2012) (Momoeda 2009)		Dienogest	Long term use	No meta-analysis, individual studies separately discussed.		
(Dragoman and Gaffield, 2016)	Systematic review - 14 studies	Endometriosis and other conditions	subcutaneously administered depot medroxyprogesterone acetate (104 mg/0.65 mL)	Safety	In endometriosis: no differences in bone mineral density among adult DMPA-SC and DMPA-IM users at 2 years of follow-up (based on 1 trial). Women with endometriosis using DMPA-SC over 6 months had minimal decreases in BMD, weight gain, few serious adverse events and experienced improved pain symptoms.		

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Petraglia, *et al.*, 2012)	open-label extension study	152 women with endometriosis, that had previously completed a 12-week, placebo-controlled study of dienogest,	DNG 2 mg/day for 36 weeks (n = 17) or 52 weeks (n = 135)	Pelvic pain (VAS) Side effects amenorrhea	improvement in pain for both the group previously treated with DNG and for the group previously treated with placebo (from 40.73 ± 21.14 to 13.49 ± 14.14 mm versus 27.89 ± 20.24 to 9.72 ± 7.44 mm, 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 %).	Long-term dienogest showed a favorable efficacy and safety profile, with progressive decreases in pain and bleeding irregularities	following up on the study of Strowitzki et al 2010
(Momoeda, *et al.*, 2009)	Cohort study	135 women with endometriosis	use of 52 weeks of Dienogest (2mg/day) was evaluated. (no control group)	Pelvic pain (VAS) Side effects Amenorrhea (5 subjective symptoms during non-menstruation (lower abdominal pain, lumbago, dyschezia, dyspareunia, and pain on vaginal examination) and 2 objective findings (induration involving the pouch of Douglas and limited uterine mobility).	A reduction in VAS score for pelvic pain was noted after 24 and 52 weeks of treatment (-22.5 ± 32.1 and -28.4 ±29.9 mm, 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.	long-term effect of dienogest on BMD was slight, whereas the efficacy increased cumulatively.	

INCLUDED AS BACKGROUND INFORMATION
(Strowitzki, *et al.*, 2010)

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	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 data are summarized in reviews, but the overall quality of the data is low due to the quality of included studies (few RCTs) and the heterogeneity with regards to interventions, comparators and outcomes Quality of evidence: ⊕⊕◯◯
Balance between desirable and undesirable outcomes	Efficacy is weight against side effects. There are some (mild) side-effects with the use of progestogens, which should be considered in decision-making (cfr GPP 19).
Balance between different outcomes	Overal, efficacy outweighs the side effects. For specific patients experiencing side effects, other treatment options should be considered. Danazol is no longer described in the guideline, as for this specific treatment, the side effects overrule the efficacy.

Patient values and preference	No data
Resource use, equity, acceptability and feasibility	It seems that progestogen treatment is acceptable and feasible in general, although the costs and availability may vary between countries.
RECOMMENDATION	It is recommended to prescribe women progestogens to reduce endometriosis-associated pain.
GPP	The GDG recommends that clinicians take the different side-effect profiles of progestogens into account when prescribing these drugs.

Progestogens – intra-uterine system

Summary of Findings Table

II.2f LNG-IUS compared to other treatment (GnRH agonist) for endometriosis-related pain

Patient or population: endometriosis-related pain
Intervention: LNG-IUS
Comparison: other treatment (GnRH agonist)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with other treatment (GnRH agonist)	Risk with LNG-IUS				
Pain (VAS, 0 to 10)	The mean pain (VAS, 0 to 10) was **2.1 to 6.1**	MD **0.03 higher** (0.53 lower to 0.59 higher)	-	126 (3 RCTs)	⊕⊕⊕◯ MODERATE [a]	
HRQoL *	The mean hRQoL was **6.8 (SD 18.2)**	MD **1.5 higher** (6.19 lower to 9.19 higher)	-	72 (1 RCT)	⊕⊕◯◯ LOW [b]	

Explanations
a. Small trials, ranging from 15 to 71 patients
b. Single trial
* Health-related QoL, assessed with: Psychological and GeneralWell-Being Index Questionnaire (PGWBI) scores

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Lan, *et al.*, 2013)	systematic review of RCTs	5 trials - 255 women	levonorgestrel-releasing intrauterine system (LNG-IUS) versus gonadotropin-releasing hormone analogue (GnRH-a)	Efficacy Safety	See SOF table Irregular bleeding, simple ovarian cysts and one-sided lower abdominal pain occurred more commonly in the LNG-IUS group (P<0.03) while vasomotor symptoms and amenorrhea were observed more frequently in the GnRH-a group (P<0.05).	The LNG-IUS had clinical efficacy equivalent to that of GnRH-a but may have some clinical advantages over GnRH-a in the treatment of endometriosis-associated symptoms.	
(Margatho, *et al.*, 2020)	RCT	103 women with endometriosis-associated chronic pelvic pain and/or dysmenorrhoea	etonogestrel-releasing subdermal implant or a 52-mg levonorgestrel-releasing intrauterine system	Efficacy: endometriosis-related pain dysmenorrhea CPP	VAS Score for dysmenorrehea at 24 mo: ENG 4.3 ± 0.4 LNGIUS : 4.4 ± 0.5 VAS Score for CPP at 24 mo: ENG 4.3 ± 0.4 LNGIUS : 4.2 ± 0.5	Both ENG and LNG-IUS significantly reduced endometriosis-related pain, dysmenorrhea and CPP for up to 24 months after device placement.	Limitation: total discontinuation rate and loss to follow-up of 32/51 (63%) in the LNG-IUS arm and 34/52 (65%) in the ENG arm.

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	Efficacy: 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. (HR)QoL is another outcome to be considered but this outcome is less reliable as there are fewer data. The safety profile is acceptable and comparable to GnRH agonist. Quality of evidence: ⊕⊕⊕◯
Balance between desirable and undesirable outcomes	Efficacy (pain outcomes) is weight against safety.
Balance between different outcomes	Efficacy seems to overrule any safety concerns.
Patient values and preference	LNG-IUS is an acceptable option for contraception, although not a valid option for all patients (cfr the discontinuation rate in Margatho, 2020)
Resource use, equity, acceptability and feasibility	Acceptable and feasible - Used for contraceptive purposes
RECOMMENDATION	**It is recommended to prescribe women a levonorgestrel-releasing intrauterine system or an etonogestrel-releasing subdermal implant to reduce endometriosis-associated pain.**

GNRH agonist

Summary of Findings Table

No meta-analysis performed for GnRH agonists versus no treatment/placebo

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Brown, *et al.*, 2010)	Systematic review	Endometriosis	GnRHa versus no treatment (1 RCT) GnRHa versus placebo (2 RCTs) GnRHas versus danazol (27 RCTs)	Relief of painful symptoms Adverse effects Quality of life	<u>GnRHa versus no treatment</u> (Fedele 1993): relief of painful symptoms (dysmenorrhoea), benefit for GnRHa : RR 3.93 (95% CI 1.37 to 11.28, P=0.01). <u>GnRHa versus placebo</u> (Bergqvist 1998) significant benefit for GnRHas for the relief of pelvic tenderness RR 4.17 (95% CI 1.62 to 10.68, P=0.003) but not for dyspareunia (RR 1.16;95%CI 0.57 to 2.34) or defecation pressure (RR 11.44; 95%CI 0.67 to 196.30). GnRHas were associated with sleep disturbances RR 2.31 (95% CI 1.33 to 4.02, P=0.003). (Miller 2000) Endometriosis Symptom Severity Score (ESSS) : significant temporary increase in ESSS with GnRHa with aMD 2.90 (95% CI 2.11 to 3.69, P<0.001). <u>GnRHas versus danazol</u> (27 RCTs) no evidence of a significant difference for the effectiveness of pain relief in dysmenorrhoea: RR0.98(95%CI0.92to1.04,P=0.53); dyspareunia : RR 1.02 (95% CI 0.93 to 1.12, P=0.69); pelvic pain RR 0.96 (95% CI 0.86 to 1.07, P=0.47); induration RR 1.10 (95%CI 0.94 to 1.29, P=0.23) and pelvic tenderness RR 0.98 (95% CI 0.88 to 1.09, P=0.70). <u>GnRHas versus IU progestagen</u> (3 RCTs)	GnRHas appear to be more effective at relieving pain associated with endometriosis than no treatment/placebo. There was no evidence of a difference in pain relief between GnRHas and danazol although more adverse events reported in the GnRHa groups. No studies compared GnRHas with analgesics.	No meta-analysis was performed for GnRHa versus placebo/no treatment

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
					no evidence of a statistically significant difference in overall pain score or rAFS scores		
(Tang, *et al.*, 2017)	RCT	50 women with stage III–IV endometriosis after laparoscopic surgery	Low dose : 2 injections 3.75-mg GnRHa + 4 injections 1.88-mg Full dose group; 6 injections 3.75-mg GnRHa	Sex hormone level symptoms of estrogen deficiency lumbar vertebrae bone density At start, 8 weeks and 20 weeks	Degree of dysmenorrhea No sign difference Sex hormones No sign difference for FSH, LH E2 sign lower in full dose group at 20weeks BMD degree of loss of BMD in the full dose group (5.6%) was higher than in the low dose group (1.2%; P < 0.05) Symptoms of perimenopause 8w: no diff 20w: symptoms improved in low dose, but not in full dose	The 1.88-mg GnRHa treatment can be used in III-IV endometriosis patients after laparoscopic surgery, to reduce perimenopausal symptoms, significantly improve bone loss, and achieve a good clinical effect.	

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	A Cochrane review of 2010 was not recently updated, and most of the included RCTs compared GnRH agonist use with danazol (an intervention no longer considered relevant). The review concluded that GnRH agonist treatments are superior to placebo and equal to danazol for relieving painful symptoms associated with endometriosis. Side effects associated with GnRH agonist include vaginal dryness, hot flushes, headaches, weight gain and acne. These considerable side-effects should be discussed with the patient when offering this treatment. The impact of GnRHa on bone mineral density can be reduced by prescribing add-back therapy. (see next section) Quality of evidence:
Balance between desirable and undesirable outcomes	Efficacy versus side effects
Balance between different outcomes	Efficacy seem to overrule side effects and the use of GnRH agonists is recommended. However, it is considered good clinical practice to give preference to medical treatments with a better side effect profile, and equal efficacy. This was articulated in a GPP. The balance of efficacy versus safety is different for adolescents and young women (considering BMD) and they are referred to specific guidance.
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	It seems that GnRH agonist treatment is acceptable and feasible in general, although the costs and availability may vary between countries.

RECOMMENDATION	It is recommended to prescribe women GnRH agonists to reduce endometriosis-associated pain, although evidence is limited regarding dosage or duration of treatment.
GPP	The GDG recommends that GnRH agonists are prescribed as second line (for example if combined oral contraceptives or a progestogen have been ineffective) due to their side-effect profile.

GNRH agonist + add-back therapy

Summary of Findings Table

II.2g GnRH agonist-only compared to GnRH agonist + add-back therapy for endometriosis-related pain

Patient or population: endometriosis patients with endometriosis-related pain
Intervention: GnRH agonist-only
Comparison: GnRH agonist + add-back therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with GnRH agonist + add-back therapy	Risk with GnRH agonist-only				
Lumbar spine BMD after treatment	The mean lumbar spine BMD after treatment was **-0.001 to 0.034**	WMD **0.03 lower** (0.05 lower to 0.02 lower)	-	932 (12 RCTs)	⨁⨁⨁◯ MODERATE [a]	
Lumbar spine BMD after 6 months of follow-up	The mean lumbar spine BMD after 6 months of follow-up was **-0.012 to 0.096**	WMD **0.02 lower** (0.03 lower to 0.01 lower)	-	431 (6 RCTs)	⨁⨁◯◯ LOW [a,b]	
Femoral neck BMD after treatment	The mean femoral neck BMD after treatment was **0.006 to 0.015**	WMD **0.01 lower** (0.02 lower to 0.01 higher)	-	116 (3 RCTs)	⨁⨁◯◯ LOW [a,b]	
Kupperman index scores after treatment	The mean kupperman index scores after treatment was **-5.2 to 10**	WMD **5.13 lower** (5.77 lower to 4.48 lower)	-	143 (3 RCTs)	⨁⨁◯◯ LOW [a,b]	
Dysmenorrhea scores after treatment	The mean dysmenorrhea scores after treatment was **1.8 to 5.8**	WMD **0.27 lower** (0.93 lower to 0.39 higher)	-	396 (5 RCTs)	⨁⨁⨁◯ MODERATE [b]	No difference between GnRH agonist-only and GnRH agonist + add-back therapy
Dyspareunia scores after treatment	The mean dyspareunia scores after treatment was **0.29 to 4.6**	WMD **0.05 higher** (0.37 lower to 0.47 higher)	-	195 (4 RCTs)	⨁⨁⨁◯ MODERATE [b]	No difference between GnRH agonist-only and GnRH agonist + add-back therapy

Explanations
a. Wide confidence intervals indicative of imprecision
b. Relatively small trials, with limited total number of patients included

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Sauerbrun-Cutler and Alvero, 2019)	Narrative review on safety	Not endometriosis specific	GnRHa With or without add-back (progestin monotherapy such as NETA, estrogen-progestin combinations, selective estrogen receptor modulators such as raloxifene, bisphosphonates, tibolone, and testosterone.)	bone loss and fracture		Short-term GnRH-a treatments combined with add-back therapy is unlikely to cause long term bone loss. Add-back therapy may minimize long term bone loss in patients using GnRH-a for extended durations. GnRH-a treatment duration should be minimized as much as possible in adolescents because they are at the peak of their bone formation and particularly susceptible to bone resorption. Add-back therapy should be used concurrently with GnRH-a and there should be no delay in starting the add-back with the start of suppression Calcium and vitamin D are recommended for all patients at risk of bone loss and should be encouraged in patients taking GnRH-a	
(Wu, *et al.*, 2014)	Systematic review	Endometriosis 13 RCT, including 945 participants	GnRHa-only versus GnRHa with add-back therapy	Clinical efficacy	Lumbar spine BMD after treatment (12 RCTs) Superior with add-back (WMD −0.03,95%CI −0.05 to −0.02, P < 0.00001) Lumbar spine BMD after 6mo FU (6RCTs) Superior with add-back (WMD −0.02,95%CI −0.03 to −0.01, P= 0.003) Femoral neck BMD after treatment (3 RCTS) : no diff Kupperman index scores after treatment (3RCTs) Superior with add-back (WMD −5.13,95%CI −5.77 to −4.48, P < 0.00001) Dysmenorrhoea scores after treatment (5 RCTs): no diff Dyspareunia scores after treatment (4 RCTs): no diff	"Add-back" therapy, based on the GnRH-a dose, does not reduce the efficacy of using GNRH-a for endometriosis. "Add-back" therapy reduced the occurrence of side effects that can occur with GnRH-a therapy alone, such as osteoporosis and menopausal syndrome. There were no statistically significant differences when comparing the effectiveness of a variety of "add-back" regimens to each other.	See SOF table

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	There is moderate quality evidence, summarized in a systematic review, that addition of add-back therapy when prescribing GnRH agonist treatment prevents bone loss, while it does not affect the efficacy of the GnRHa treatment. Quality of evidence: ⊕⊕⊕◯ (systematic review of RCTs, fors ome of the outcomes, more data could still be helpful)
Balance between desirable and undesirable outcomes	The addition of add back therapy is considered beneficial, with no shown undesirable effects.
Balance between different outcomes	Safety (BMD) is considered the most relevant outcome. With no difference in efficacy, GnRH agonist +add back is clearly superior to GnRH agonist alone and recommended
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	It seems that GnRH agonist + add back treatment is acceptable and feasible in general, although the costs and availability may vary between countries.
RECOMMENDATION	**Clinicians should consider prescribing combined hormonal add-back therapy alongside GnRH agonist therapy to prevent bone loss and hypoestrogenic symptoms.**

GNRH antagonist

Summary of Findings Table

II.2h GnRH antagonist compared to no treatment/placebo for endometriosis-related pain

Patient or population: patients with endometriosis-related pain
Intervention: GnRH antagonist
Comparison: no treatment/placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no treatment/placebo	Risk with GnRH antagonist				
Clinically meaningful reduction in dysmenorrhea follow up: 3 months	196 per 1,000	**470 per 1,000** (333 to 607)	**RR 2.4** (1.7 to 3.1)	621 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	Data for dose GnRH antagonist (dose 150 mg once daily) versus placebo in Elaris Endometriosis-I trial
Clinically meaningful reduction in non-menstrual pelvic pain follow up: 3 months	365 per 1,000	**510 per 1,000** (401 to 620)	**RR 1.4** (1.1 to 1.7)	621 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	Data for dose GnRH antagonist (dose 150 mg once daily) versus placebo in Elaris Endometriosis-I trial
Clinically meaningful reduction in dysmenorrhea follow up: 6 months	231 per 1,000	**416 per 1,000** (301 to 532)	**RR 1.8** (1.3 to 2.3)	619 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	Data for dose GnRH antagonist (dose 150 mg once daily) versus placebo in Elaris Endometriosis-I trial
Clinically meaningful reduction in non-menstrual pelvic pain follow up: 6 months	349 per 1,000	**454 per 1,000** (349 to 559)	**RR 1.3** (1.0 to 1.6)	619 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	Data for dose GnRH antagonist (dose 150 mg once daily) versus placebo in Elaris Endometriosis-I trial

Explanations
a. Single trial – confirmed in a second trial in the same publication

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Taylor, *et al.*, 2017)	RCT	A total of 872 women with surgically diagnosed endometriosis and moderate or severe endometriosis-associated pain underwent randomization 653 (74.9%) and 632 (77.4%), resp, completed the intervention.	150 mg once daily (lower-dose group) and 200 mg twice daily (higher-dose group) — as compared with placebo	Primary efficacy end points : - clinical response with respect to dysmenorrhea - clinical response with respect to nonmenstrual pelvic pain at 3 months.	Both higher and lower doses of elagolix were effective in improving dysmenorrhea and nonmenstrual pelvic pain during a 6-month period in women with endometriosis-associated pain. The two doses of elagolix were associated with hypoestrogenic adverse effects: hot flushes (mostly mild or moderate), higher levels of serum lipids, and greater decreases from baseline in BMD		(data for the lower dose from Elaris I are shown in the SOF TABLE)

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Donnez, *et al.*, 2020)	RCT	327 Women aged 18–45 years with surgically confirmed endometriosis and moderate-to-severe pain	50, 75, 100, or 200 mg linzagolix (or matching placebo) administered once daily for 24 weeks.	number of responders (≥30% reduction in overall pelvic pain) after 12 weeks. Other endpoints dysmenorrhea, non-menstrual pelvic pain, serum estradiol, amenorrhea, quality of life (QoL) measures, and BMD [Mean percent (95% CI)]	34.5%, 49.4%, 61.5%, 56.4%, and 56.3% in the placebo, 50 mg, 75 mg, 100 mg, and 200 mg groups, resp. all groups (but 50mg) significant difference vs placebo women experiencing a reduction of ≥30% in DYS and a reduction of ≥30% in NMPP at week 12: 43.3% (ns) and 46.2% (ns) in the 50 mg group, 68.2% (P<.001) and 58.5% (P=.017) in the 75 mg group, 68.6% (P<.001) and 61.5% (P=.022) in the 100 mg group, and 78.9% (P<.001) and 47.7% (ns) in the 200 mg group, compared with the placebo percentages of 28.5% and 37.1%. The percentages of women with a ≥30% reduction in OPP at week 24 were 52.5%, 70.8%, 66.7%, 66.7%, and 77.3% in the 50 mg, 75 mg FD, 75 mg TD, 100 mg, and 200 mg groups, respectively BMD changes for lumbar spine from baseline to week 24 in the 50, 75 (FD), 75 (TD), 100, and 200 mg dose groups were 0.14% (-0.83, 1.11), -0.80% (-1.57, -0.03), -1.0% (-1.71, -0.29), -1.37% (-.14, -0.59), and -2.60% (-3.56, -1.65), resp. BMD change in femoral neck and total hip showed a similar pattern but with generally smaller changes from baseline.	Linzagolix significantly reduced endometriosis-associated pain and improved QoL at doses of 75-200 mg and decreased BMD dose-dependently.	
(Osuga, *et al.*, 2020)	RCT	Adult premenopausal women with endometriosis who had dysmenorrhea and endometriosis-associated pelvic pain.	12-week treatment period, patients received relugolix 10 mg (n=103), 20 mg (n=100), or 40 mg (n=103) as a daily oral dose; placebo (n = 97) as a daily oral dose; or leuprorelin 3.75 mg (n=80) as a monthly subcutaneous injection.	pelvic pain (VAS) Adverse events	The mean changes in mean visual analog scale score for pelvic pain were –3.8 mm in the placebo group; –6.2, –8.1, and –10.4 mm in the relugolix 10-mg, 20-mg, and 40-mg groups; respectively; and –10.6 mm in the leuprorelin group. The major adverse events with relugolix were hot flush, metrorrhagia, menorrhagia, and irregular menstruation, and BMD decrease in a dose–response manner, which were also observed in the leuprorelin group with a frequency comparable with that in the 40-mg group.	Oral administration of relugolix alleviated endometriosis-associated pain in a dose–response manner and was generally well tolerated. Relugolix 40 mg demonstrated efficacy and safety comparable with those of leuprorelin.	

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	Emerging evidence from RCTs on oral GnRH antagonists (elagolix, relugolix and linzagolix) suggest that they are effective in the relief of endometriosis-associated pain. The 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. 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. Quality of evidence: ⊕⊕⊕◯
Balance between desirable and undesirable outcomes	Efficacy versus side effects
Balance between different outcomes	Efficacy seem to overrule side effects and the use of GnRH antagonists is recommended. The side effect profile seems to be similar as for GnRH agonists and the same considerations apply.
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	It seems that GnRH antagonist treatment is acceptable and feasible in general, although the costs and availability may vary between countries.
RECOMMENDATION	**It is recommended to prescribe women GnRH antagonists to reduce endometriosis-associated pain, although evidence is limited regarding dosage or duration of treatment.**
GPP	**The GDG recommends that GnRH antagonists are prescribed as second line (for example if combined oral contraceptives or a progestogen have been ineffective) due to their side-effect profile.**

Aromatase Inhibitors

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Ferrero, *et al.*, 2011)	Review	Endometriosis (10 studies)	oral letrozole plus norethisterone acetate (NEA) or desogestrel, or anastrozole as vaginal suppository (250µg daily) or orally (1mg daily) in combination with OCP	endometriosis-associated pain symptoms (5 observational studies, 1 patient-preference trial and 1 RCT) (FU mostly 6 months) Prevention of symptom recurrence after surgery (3 RCTs) (data not reported as not relevant for the key question)	All studies demonstrated that AIs combined with either progestogens, OCP or GnRHagonist reduce the intensity of pain symptoms caused by endometriosis 2 observational studies showed that the administration of AIs improves quality of life The effect of AIs on the volume of rectovaginal endometriotic nodules remains unclear.		No meta-analysis performed
(Almassinokiani, *et al.*, 2014)	RCT	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 surgery	Letrozole plus OCP (n=25) or only OCP (n=26) for 4 months	endometriosis-related pelvic pain Dysmenorhea score Dypareunia score Noncyclic pelvic pain score (all assessed 4 months after treatment)	dyspareunia, dysmenorrhea and pelvic pain 4 months after the laparoscopic surgery declined significantly in both groups but the difference between results of the two groups was not significant.	No significant difference in outcome between the 2 groups and the results of both treatment modalities were similar. Letrozole did not affect the outcome.	
(Agarwal and Foster, 2015)	Cohort study	8 consecutive women with a total of 14 endometriomas	3-month off-label course of daily 5mg letrozole with 5mg norethindrone acetate add-back	Endometrioma size/volume Pain score	Mean endometrioma diameter decreased 50% from 4.6 ± 1.6 cm, range from1.7 to 7.4 cm, to 2.3 ± 1.6 cm, range 0–4.3 cm(p< 0.01) Mean endometrioma volume reduction of 75% from 60.1 ± 58.7cm3,range 2.6–212.2 cm3,to 15.0 ± 16.4cm3,range 0–51 cm3 (p<0.01). Mean dyspareunia score decreasing from 2 to 0 and mean dyspareunia and nonmenstrual pelvic pain scores decreasing from1 to 0.	A 3month course of aromatase inhibition plus progestin significantly decreases ovarian endometrioma size.	

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	The evidence consists of a systematic review from 2011, including mostly non-randomized controlled studies and case reports in women with rectovaginal endometriosis or women that are refractory to previous surgical and medical treatment, and 2 more recent studies. Evidence on the long-term effects of aromatase inhibitors is lacking. Quality of evidence; ⊕⊕◯◯ 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. Still, side effects (vaginal dryness, hot flushes, diminished bone mineral density) are considered severe.
Balance between desirable and undesirable outcomes	Efficacy with regards to symptom relief should be weight against side effects
Balance between different outcomes	Aromatase inhibitors are considered an effective treatment; However, the benefits only outwieigh the side effects in women in whom all other options for medical or surgical treatment are exhausted (ie those refractory to other medical or surgical treatment)
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	Aromatase inhibitors are not available (even off-label) in some countries.
RECOMMENDATION	**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.**

QUESTION II.3 IS SURGERY EFFECTIVE FOR TREATMENT OF PAIN ASSOCIATED WITH ENDOMETRIOSIS?

Surgery versus diagnostic laparoscopy or medical treatment

Summary of Findings Table

II.3a Laparsocopy compared to diagnostic laparsocopy for endometriosis-associated pain

Patient or population: patients with endometriosis-associated pain
Intervention: laparsocopy
Comparison: diagnostic laparsocopy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with diagnostic laparsocopy	**Risk with laparsocopy**				
Overall pain scores follow up: 6 months	The mean overall pain scores was **1**	MD **0.9 higher** (0.31 higher to 1.49 higher)	-	16 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	Based on Bafort 2020
Overall pain scores follow up: 12 months	The mean overall pain scores was **0.95**	MD **1.65 higher** (1.11 higher to 2.19 higher)	-	16 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	Based on Bafort 2020
Quality of life EQ-5D index summary follow up: 6 months	The mean quality of life EQ-5D index summary was **0.74**	MD **0.03 higher** (0.12 lower to 0.18 higher)	-	39 (1 RCT)	⨁⨁◯◯ LOW [c]	Based on Bafort 2020

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Single trial
b. Downgraded once for high risk of attrition bias.
c. Downgraded twice for imprecision – limited number of participants or wide confidence interval crossing the line of no effect, or both.

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Bafort, *et al.*, 2020a)	SR	4 RCTs compared laparoscopic ablation or excision with diagnostic laparoscopy only (Gad 2012; Marcoux 1997; Moini 2012; Tutunaru 2006). 2 RCTs compared laparoscopic excision with diagnostic laparoscopy (Abbott 2004;Jarrell 2005)	laparoscopic intervention versus diagnostic laparoscopy.	Overall pain (Live birth)	See Summary of Findings Table	Compared to diagnostic laparoscopy only, it is uncertain whether laparoscopic surgery reduces overall pain associated with minimal to severe endometriosis.	Individual studies included below
(Abbott, *et al.*, 2004)	RCT	39 women with histologically proven endometriosis completed the 12-month study. During the 12-month study period, one woman in each group commenced taking the oral contraceptive pill for contraceptive purposes.	laparoscopic intervention (n=20) versus diagnostic laparoscopy (n=19). Diagnostic laparoscopy group also received delayed laparoscopic surgery After 6 months, repeat laparoscopy was performed, with removal of any pathology present.	changes from baseline values of visual analogue pain scores, validated quality-of-life instruments (EQ-5D and SF-12), and sexual activity questionnaire scores. Patients and assessors of outcomes were blinded to the treatment-group assignment.	Improvement in pain: 6(32%) of diagn lap group vs 16/(80%) in lap group No changes in pain (or worsening): 13 (68%) vs 4(20%) Mean difference in VAS score at 12mo between the 2 groups: Dysmenorrhea: -1.1 (-20.8, 18.6), P=.91 Nonmenstrual pelvic pain: 3.4 (-11.8, 18.7), P=.65 Dyspareunia -6.5 (-24.7, 11.5), P=.47 Dyschesia -3.1 (-20.6, 14.5), P=.72 After surgery, there was a significant improvement in the EQ-5D VAS and both mental and physical components of the SF-12. This change was not reported in the diagnostic lap group	Laparoscopic excision of endometriosis is more effective than placebo at reducing pain and improving quality of life. Approximately 20% of women do not report an improvement after surgery for endometriosis	Included in (Bafort, *et al.*, 2020a)
(Jarrell, *et al.*, 2005)	RCT	29 Patients requiring a laparoscopy for severe pelvic pain were eligible. 16 completed the full year of follow up Laparoscopy: Excision group rAFS stage I (2/15); II (10/15); III (3/15) Control group rAFS stage I (4/14); II (10/14) Lower proportions of nodular endometriotic disease at time of surgery ($p < .025$)	Laparoscopic intervention (excision) (n=9) Versus diagnostic laparoscopy + expectant management (n=7).	Daily pain scales for 1 month preoperatively and quarterly for 1 year postop. Subjects were blinded to their treatment allocation for 1 year.	Recorded pain was significantly reduced at 1 year ($p < 0.05$), with no significant difference between the excision and control groups	Laparoscopy with diagnostic biopsy alone is associated with a significant reduction in pain for up to 1 year postoperatively	Included in (Bafort, *et al.*, 2020a)

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Sutton, *et al.*, 1994)	RCT	63 patients with pain (dysmenorrhoea, pelvic pain, or dyspareunia) and minimal to moderate endometriosis	laser ablation of endometriotic deposits and laparoscopic uterine nerve ablation or expectant management. The women were unaware of the treatment allocated as was the nurse who assessed them at 3 and 6 months after surgery.	Improvement or resolution of pain symptoms assessed subjectively and by visual analogue score. Pain symptoms were recorded subjectively and by visual analogue scale.	Laser laparoscopy results in statistically significant pain relief compared with expectant management at 6 months after surgery. 62.5% of the lasered patients reported improvement or resolution of symptoms (22.6% in expectant group). If patients with mild and moderate disease only are included, 73.7% of patients achieved pain relief. There were no operative/laser complications.	Laser laparoscopy is a safe, simple, and effective treatment in alleviating pain symptoms in women with stages I, II, and III endometriosis.	

Impact of surgery on QoL

Summary of Findings Table

Studies report post-operative pain scores with pre-operative scores. None of the studies compare 2 interventions and hence a SOF table is not relevant

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Arcoverde, *et al.*, 2019)	SR	Included 38 studies that assessed QoL before and after surgery including 21 prospective cohorts, 8 RCTs, 8 retrospective cohorts and 1 nonrandomised study	Laparoscopic/robotic surgery,	HRQOL using SF-36, SF-12, EHP30 or EQ-5D	8 studies including 983 patients with **all types of endometriosis** with F/U of 3-37 months, 3 studies (Abbott et al 2003, Abbott et al 2004, Soto et al 2017) with 269 patients were metaanalysed for MCS and PCS, surgery significantly improved MCS (OR 0.21, 95% CI 0.05-0.38), but not PCS. Two studies (Roman JD 2010, Narwani 2017) using EQ-5D including 443 patients showed improvements in all domains, except anxiety. One study (Valentin et al 2017) 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 = .002) and MCS (40.6 ± 12.21 vs 45.0 ± 11.3; p < .001) , but only 16% of women had a 5 point of more improvement in their scores.		
(Franck, *et al.*, 2018)	SR	12 studies	laparoscopic surgery	quality of sexual life (QoSL)	endometriosis negatively affects several domains of female sexual functioning, such as pleasure, frequency of sexual intercourse,	Laparoscopic excision of endometriosis can improve QoSL. However, there is a need for	meta-analysis could not be performed due to heterogeneity

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
					comfort, desire, orgasm and satisfaction with sex. In contrast, six of the seven validated questionnaires used in the 12 studies included in our analysis identified improvements in sexual function following laparoscopic surgery for endometriosis regardless of location, severity of the disease and hormonal treatment.	randomized controlled trials based on a new validated questionnaire regarding specifically QoSL in association with endometriosis.	

INCLUDED AS BACKGROUND INFORMATION
(Abbott*, et al.*, 2004, Abbott*, et al.*, 2003, M F*, et al.*, 2017, Roman, 2010b, Soto*, et al.*, 2017, Valentin*, et al.*, 2017, Vercellini*, et al.*, 2003a).

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	Surgery versus diagnostic laparoscopy or medical treatment: very little data included in the Cochrane review **(very low quality evidence)** Impact of surgery on QoL: Arcoverde et al 2018 show benefit of surgery for endometriosis in general. (moderate to low quality evidence) Studies published so far have limited follow up of 6-12 months and have shown benefit in that timeframe, some studies showing this benefit is retained to 7 months. There is limited knowledge from non-RCTs on whether the benefit is retained with longer term follow up. Quality of evidence: ⊕⊕◯◯ (combination from data on pain scores (Cochrane) and the Arcoverde review)
Balance between desirable and undesirable outcomes	Efficacy for pain and QoL should be weight against possible surgical complications. There are reassuring data with regards to the complication rate associated with surgery for endometriosis (Bafort*, et al.*, 2020a, Byrne*, et al.*, 2018b, Chapron*, et al.*, 1998)
Balance between different outcomes	The GDG considered it reasonable that clinicians offer surgical treatment as an option for relieving endometriosis-associated pain symptoms based on its efficacy and limited complications.
Patient values and preference	There are no data supporting a single treatment pathway applicable for all women with endometriosis. As such, treatment options are presented as options, with room for consideration of individual patient values and preferences
Resource use, equity, acceptability and feasibility	Surgery is considered acceptable and feasible, although it may require more resources compared to medical treatment
RECOMMENDATION	**It is recommended to offer surgery as one of the options to reduce endometriosis-associated pain.**

Ablation versus excision of endometriosis

Summary of Findings Table

II.3b Excision compared to ablation for endometriosis

Patient or population: endometriosis
Intervention: Excision
Comparison: Ablation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with ablation	Risk with excision				
Reduction in VAS Score for Dysmenorrhea	The mean reduction in VAS Score for Dysmenorrhea was **1.5 to 2.0**	MD **0.99 higher** (0.02 lower to 2 higher)	-	198 (2 RCTs)	⨁⨁◯◯ LOW [a,b]	Barton Smith 2010 and Healey 2010 in Pundir 2017
Reduction in VAS Score for Dyschezia	The mean reduction in VAS Score for Dyschezia was **0.7 to 1.11**	MD **1.31 higher** (0.33 higher to 2.29 higher)	-	198 (2 RCTs)	⨁⨁◯◯ LOW [a,b]	Barton Smith 2010 and Healey 2010 in Pundir 2017
Reduction in VAS Score for Chronic Pelvic Pain	The mean reduction in VAS Score for Chronic Pelvic Pain was **3.5**	MD **2.57 higher** (1.27 higher to 3.87 higher)	-	95 (1 RCT)	⨁⨁◯◯ LOW [a,c]	Barton Smith 2010 in Pundir 2017
Reduction in VAS scores of dyspareunia	The mean reduction in VAS scores of dyspareunia was **1.27 to 1.8**	MD **0.96 higher** (0.07 lower to 1.99 higher)	-	198 (2 RCTs)	⨁⨁◯◯ LOW [a,b]	Barton Smith 2010 and Healey 2010 in Pundir 2017

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgraded once for high risk of attrition bias.
b. Downgraded for imprecision – limited number of participants and 95% confidence intervals crossed the threshold.
c. Single small RCT

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Pundir, *et al.*, 2017)	SR	3 studies, of which 2 (Barton-Smith, 2010, Healey, *et al.*, 2010) are included in meta-analysis	laparoscopic excision versus ablation	Reduction in VAS Score for Dysmenorrhea Reduction in VAS Score for Dyspareunia, Dyschezia, Chronic Pelvic Pain , Pelvic Pain , Reduction in EHP-30 Core Pain Score	See SOF table		The results from barton-Smith are published in a doctoral thesis only[1]
(Wright, *et al.*, 2005)	RCT	24 Women with a history of dysmenorrhea, dyspareunia, dyschezia, pelvic pain, or backache Severity of disease: rASRM 1: mild, superficial	Monopolar excision with 3-mm monopolar diathermy scissors with a combination of 90Wpure cut and 50Wcoagulation vs Monopolar diathermy ablation at coagulation current of 50W.	Mean change in questionnaire scores Symptoms: pelvic pain, dysmenorrhea, dyspareunia, dyschezia, constipation, diarrhea, cramps exercise pain, back pain, fatigue. Signs: uterine mobility, tenderness, adnexal pain, ultrasound scan, pouch of Douglas.	The study reported that both treatment modalities produced good symptomatic relief and a reduction in pelvic tenderness (67%). There was no significant difference between the 2 procedures for any of the individual questionnaire items. A high pain score before treatment was suggested to be a good predictor of appreciable improvement after surgery.		Included in the review of Pundir, but not in the meta-analysis because of incomplete data
(Healey, *et al.*, 2014)	Follow-up study of (Healey, *et al.*, 2010)	By 5 years after surgery questionnaires had been returned from 42 sub-jects who underwent ablation (out of 89) and 40 subjects who under-went excision (out of 89).	laparoscopic excision versus ablation 5-year follow up	Change in pain VAS scores and rates of pregnancy, repeat surgery, and use of hormone therapy	significantly greater reduction in dyspareunia VAS scores was observed in the excision group (6.0[0-10.0]) vs ablation (3.2[-4.3-10.0]) (p = .007 at multivariate analysis). Minor difference in abdominal pain reduction (for excision) More women in the ablation group continued to receive medical treatment of endometriosis at 5 years (p 5 .004). (31% versus 20%) No differences in other outcomes	Surgical treatment of endometriosis provides symptom reduction for up to 5 years. In some limited areas such as deep dyspareunia, excision is more effective than ablation	

INCLUDED AS BACKGROUND INFORMATION
(Barton-Smith, 2010, Healey, *et al.*, 2010)

[1] The GDG has revised the thesis and considers it a well designed study. The authors clarified that it was not published due to a disagreement between 2 supervisors. Although not peer reviewed, the data were considered of sufficient quality for the Cochrane review and the guideline

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	The limited available evidence shows that at 12 months post surgery, symptoms of dysmenorrhea, dyschezia, and chronic pelvic pain secondary to endometriosis showed a significantly greater improvement with laparoscopic excision compared with ablation Quality of evidence: ⊕⊕◯◯
Balance between desirable and undesirable outcomes	None of the studies reported adverse events for either of both techniques. There is no evidence of more complications or other undesirable outcomes linked to either surgical technique
Balance between different outcomes	The effect on pain was considered the most relevant outcome
Patient values and preference	Patients seem to have a preference for excision, although unclear what this preference is based on.
Resource use, equity, acceptability and feasibility	There is no indication than one surgical technique should be preferred over the other based on resource use, equity, acceptability or feasibility, although the expertise of the clinician with either technique should be considered in decision making.
RECOMMENDATION	**When surgery is performed, clinicians may consider excision instead of ablation of endometriosis to reduce endometriosis-associated pain.**

Superficial peritoneal endometriosis

No trials

Surgical interruption of pelvic nerve pathways

Summary of Findings Table

It was decided not to formulate a recommendation LUNA or PSN and hence considered not required to prepare a SOF table

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Proctor, *et al.*, 2005)	SR	Candiani 1992 Randomised 78, analysed 71 71 women undergoing laparoscopic surgery for stage III or IV endometriosis and moderate or severe midline or midline +lateral pelvic pain	LUNA vs control Presacral neurectomy with conservative surgery for endometriosis vs conservative surgery for endometriosis	12 mo Dysmenorrhoea, measured by 0-10 scale and multidimensional scale including limitation of work ability, systemic symptoms and need for analgesics, data reported as mild, moderate severe Adverse effects Preop vs 12 month postop	LUNA vs control Pain relief at 6 months Johnson 2004 6/30 vs 11/31, OR 0.45 (0.14-1.45) Sutton 2001 18/26 vs 17/23 OR 0.79 (0.23-2.77) 3rd study included in the meta-analysis is not endometriosis Pain relief at 12 months (Johnson 2004, Vercellini 2003) 108 vs 109 pts OR 0.77 (0.3-1.39) Pain relief upto 36 months (Vercellini 2003) 59 vs 57 pts OR 0.84 (0.39-1.80) PSN vs control Pain relief at 6 months (Zullo 2003) 63 vs 63 pts OR 4.52 (1.84-11.02) Pain relief at 12 months (Candiani 1992 and Zulo 2003) 98 vs 99 pts OR 3.1 (1.59-6.21) Adverse effects (Candiani 1992) 35 vs 36 pts OR 14.57 (5.04-42.15) ADVERSE EVENTS: 13 women with constipation, 3 with urinary urgency, 2 with painless first stage of labour No major adverse effects, 2 women who did not have LUNA had repeat catheterisation within 24 hours	There is no evidence to use UNA for treatment of endometriosis There is some evidence to use PSN for treatment of endometriosis relate pain, data suggest this may be specific to laparoscopy and midline pain only PSN requires high degree of skill and carries more potential hazards	PSN in addition to conservative laparoscopic surgery for endometriosis related pain is beneficial, compared to conservative surgery only, whilst UNA does not have any benefit as an additional procedure. PSN is associated with increased risk of adverse effects such as bleeding, constipation, urinary urgency and painless first stage of labour.
		Johnson 2004, 123 women, 108 with dysmenorrhoea, 61 with endometriosis Women with CPP (dysmenorrhoea, nonmenstrual pelvic pain, dyschesia, deep dyspareunia for > 6 mo)	LUNA and conservative surgery for endometriosis vs conservative surgery for endometriosis	12 mo Changes in pain, whether there was a decrease of >50% in VAS, whether there was a difference in median VAS change Numbers needing further surgery Numbers needing medical treatment for pain Adverse effects			
		Sutton 2001, 51 recruited, 46 analysed 46 women undergoing laparoscopic laser surgery for stage I-III endometriosis	LUNA and conservative surgery for endometriosis vs conservative surgery for endometriosis	6 months Dysmenorrhoea as measured by VAS and pain scoring questionnaire at 3 and 6 months Adverse effects			
		Tjaden 1990 26 women, 8 randomised, 18 non-randomised, undergoing laparotomy for resection of endometriosis associated with moderate to severe dysmenorrhoea	PSN with resection of endoemtriosis vs resection of endometriosis only	6 months, but upto 42 months F/U Pain relief reported as the number of with women with pain relief in 3 locations Adverse effects			
		Vercellini 2003, 180 recruited, 116 analysed 116 women undergoing first line operative laparoscopy for minimal to severe endometriosis, with symtomps >6 months	Uterosacral lig resection with conservative laparoscopic surgery for endometriosis vs conservative laparoscopic surgery	6 and 12 months Dysmenorrhoea as 100 mm VAS, Frequency as number of episodes per cycle for dysmen and CPP Hospital anxiety and depression scale Sexual rating scale SF36 Adverse effects			
		Zullo 2003, 141 randomised, 121 analysed 126 fertile age women undergoing conservative laparoscopic surgery for symptomatic endometriosis unresponsive to medical treatment for > 6months	Laparoscopic PSN with conservative surgery for endometriosis vs conservative surgery for endometriosis	6 and 12 months Dysmenorrhoea as 100 mm VAS, Frequency as number of episodes per cycle for dysmenorrhea and CPP Adverse effects			
(Miller, *et al.*, 2020)	SR and meta-analysis	7 studies with 8 group comparisons representing 503 women (250 PN; 253 Control) were included	conservative surgery with presacral neurectomy versus surgery without	risk of treatment failure Operative complications	<u>risk of treatment failure:</u> RR 0.43 (95% CI: 0.30, 0.60; p < 0.001) suggesting lower risk with PSN	In well-selected patients, conservative surgery with adjunctive PN may provide greater relief from midline pain and a similarly low rate	Included studies overlapping with Proctor 2005 : Candiani, 1992

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
			presacral neurectomy	postoperative complications including constipation, urinary incontinence, and reoperation treatment failure = proportion of women in which surgery failed to adequately resolve midline pain, evidenced by continuation or recurrence of moderate or severe pain during follow-up.	Complications (6 studies) RR 3.00 (0.13-72.2) Higher with PSN (complication rate 1/175 in PSN vs 0/171 in control group Constipation (2studies) RR 10.62 (1.36, 82.8) Higher with PSN Reoperation (2studies) RR 1.25 (0.31, 5.06) Higher with PSN Urinary incontinence (1study) RR 7.00 (0.37, 133) Higher with PSN	of operative complications relative to conservative surgery alone but may increase the risk of constipation postoperatively.	Tjaden, 1990a Zullo, 2003/ Studies not included in Proctor: Garcia, 1977 Liu, 2011 Polan, 1980 Puolakka, 1980 Tjaden, 1990b Zullo 2004

INCLUDED AS BACKGROUND INFORMATION
(Candiani, *et al.*, 1992, Johnson, *et al.*, 2004, Sutton, *et al.*, 2001, Tjaden, *et al.*, 1990, Vercellini, *et al.*, 2003a, Zullo, *et al.*, 2003)

It was decided not to formulate a recommendation LUNA or PSN, but to formulate the following conclusions:

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.

Ovarian endometrioma - Surgical technique

Summary of Findings Table

II.3c Cystectomy compared to drainage and coagulation for endometrioma

Patient or population: endometrioma
Intervention: cystectomy
Comparison: drainage and coagulation

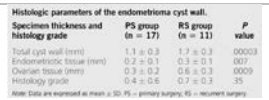
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with drainage and coagulation	Risk with cystectomy				
Recurrence of dysmenorrhea	553 per 1,000	**157 per 1,000** (69 to 320)	**OR 0.15** (0.06 to 0.38)	104 (2 RCTs)	⨁⨁◯◯ LOW [a,b]	
Recurrence of dyspareunia	750 per 1,000	**194 per 1,000** (29 to 605)	**OR 0.08** (0.01 to 0.51)	27 (1 RCT)	⨁⨁◯◯ LOW [b,c]	
Recurrence of non- menstrual pelvic pain	529 per 1,000	**101 per 1,000** (22 to 387)	**OR 0.10** (0.02 to 0.56)	37 (1 RCT)	⨁⨁◯◯ LOW [b,c]	
Relief from pelvic pain	1,000 per 1,000	**0 per 1,000** (0 to 0)	not estimable	164 (2 RCTs)	⨁⨁◯◯ LOW [a,b]	Both excision and drainage and coagulation of endometrioma treated the symptom 100% effectively in all cases, after short-term follow up.
Requirement for further surgery	229 per 1,000	**59 per 1,000** (15 to 190)	**OR 0.21** (0.05 to 0.79)	100 (1 RCT)	⨁⨁◯◯ LOW [b,c]	
Recurrence of endometrioma follow up: 12-24 months	263 per 1,000	**127 per 1,000** (60 to 249)	**OR 0.41** (0.18 to 0.93)	164 (2 RCTs)	⨁⨁◯◯ LOW [b,c]	Data from Hart 2008
Recurrence of endometrioma follow up: 12 months	316 per 1,000	**111 per 1,000** (36 to 300)	**OR 0.27** (0.08 to 0.93)	74 (1 RCT)	⨁⨁◯◯ LOW [c]	Data from Carmona 2011 (OR calculated)
Recurrence of endometrioma follow up: 60 months	368 per 1,000	**222 per 1,000** (90 to 442)	**OR 0.49** (0.17 to 1.36)	74 (1 RCT)	⨁⨁◯◯ LOW [c]	Data from Carmona 2011 (OR calculated)

Explanations
a. Data based on 2 small RCTs
b. Possible performance bias
c. Single small RCT

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
PAIN / DISEASE RECURRENCE							
(Hart, *et al.*, 2008)	Meta-analysis	ovarian endometriotic cysts (3 cm or larger) 2 RCTs, 164 patients	laparoscopic excision Versus drainage and coagulation by bipolar diathermy	Relief of pain Recurrence of pain Recurrence of endometrioma Need for reoperation	See Summary of Findings Table	There is good evidence that excisional surgery for endometrioma provides a more favourable outcome than drainage and ablation with regard to the recurrence of the endometrioma, recurrence of pain symptoms, and subsequent spontaneous pregnancy in women who were previously subfertile.	Search was updated in 2010, but no new studies were identified
(Carmona, *et al.*, 2011)	Prospective randomized clinical trial.	90 women with ovarian endometriomas.	cystectomy versus laser vaporization	Recurrence, evaluated by US Time to recurrence Assessment at 12 and 60 months of follow-up.	See Summary of Findings Table Time to recurrence (months) ; Cyst : 18.1 ± 10.1 Laser: 7.5 ± 4.3 p<.003	The comparison between laparoscopic laser ablation and laparoscopic cystectomy for ovarian endometriomas after long-term follow-up showed earlier recurrences and a higher recurrence rate in the laser group, although at 5 years of follow-up there were no statistically significant differences.	
(Candiani, *et al.*, 2020)	Retrospective study with prospective recording of data.	125 women with symptomatic endometriomas. symptomatic (pain and/or infertility) patients of reproductive age (<40years), primary unilateral or bilateral endometriomas identified by TVUS, and largest diameter of the endometrioma ≥ 3 cm and ≤8 cm.	laparoscopic stripping technique (n=64) or cyst vaporization with CO2 fiber laser (n=61).	recurrence of the cyst recurrence of symptoms. Endometrioma recurrence was defined as an ovarian cyst (>10 mm) with a typical aspect arising on the operated ovary identified by TVUS. Total follow up : 3 years mean follow-up was 29 ± 13 months (range, 13–49)	Recurrence of cyst: Strip : 4 (6.3%) Laser: 3 (4.9%) P=0.74 recurrence of symptoms. Strip : 5 (7.8%) Laser: 6 (9.8%) P=0.67 Mean endometrioma diameter > 5 cm at the time of surgery was identified as the only independent poor prognostic indicator for cyst recurrence (p = .008; OR, 2.21; 95%CI 1.19–3.32). presence of DE at surgery (p=.032; OR 4.60; 95%CI 1.14–18.57) and discontinuation of hormonal treatment (p= .015; OR, 3.18; 95%CI 1.25–8.06) were independent poor	one-step CO2 fiber laser vaporization may be effective for endometrioma treatment because it is associated with recurrence rates comparable with those occurring after cystectomy, with the advantage of being an ovarian tissue-sparing technique.	

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
					prognostic indicators for pain recurrence		
(Muzii, *et al.*, 2016a)	RCT	51 patients with bilateral endometriomas larger than 3 cm. reproductive age with pelvic pain and/or infertility	Stripping technique and the combined excisional/ablative technique one ovary was randomized to the stripping technique and the contralateral to the combined excisional/ablative technique.	endometrioma recurrence ovarian reserve (see below) Post-operative follow-up was performed at 1, 3 and 6 months after surgery	endometrioma recurrence – 6mo Strip 3/51 (5.9%) Comb 1/51 (2.0%) OR 3.00 (0.24 to 157.5) P=0.62 2 and 2 pregnancies occurred before the 3 and 6-month visit, resp, whereas 2 and 5 patients were started on medical treatment for pain recurrence before the 3 and 6-month visit, resp.	There is no evidence that the combined excisional/ablative technique is better than the traditional stripping technique, as similar recurrence rates were observed for the two techniques.	
(Shaltout, *et al.*, 2019)	RCT	200 women with endometrioma	• drainage • cystectomy • drainage + insertion of Surgicel inside the cyst cavity • cystectomy + insertion of Surgicel inside the remaining ovarian tissues	Recurrence ovarian reserve (AMH/AFC) (see below) FU 24 months	Recurrence Drain; 13/48 Cyst: 11/45 Drain+SURGICEL: 5/46 Cyst+SURGICEL; 4/44 P= 0.004 for surgicel vs no surgical NS for drain vs cyst	Surgicel reduces effectively the recurrence risk of endometriomas and its use during laparoscopic drainage is an effective alternative for traditional laparoscopic cystectomy with minimal affection of the patient ovarian reserve.	
(Muzii, *et al.*, 2005)	RCT	48 patients with ovarian endometrioma	direct stripping compared to circular excision at the initial adhesion site followed by stripping	Operative time and technical difficulties	Total laparoscopic time (mean ± SD) Not significantly different Surgical difficulty Direct stripping was more difficult in 1 of the 2 trials No intra-operative or post-operative severe complications	easier to remove the cyst with the circular excision technique but duration of operation, intraoperative complications and post-operative endometrioma recurrence rates were similar	
(Mossa, *et al.*, 2010)	RCT	92 women with endometrioma greater than or equal to 3 cm, 2 dropouts, Cyst size was significantly larger in the circular excision group	Direct stripping at the original adhesion site (n=47) vs circular excision at the initial adhesion site followed by stripping (n=43) • Follow up 4 and 12 months for recurrence, 36 months for pregnancy	Surgical time Time of haemostasis Accuracy Complications Recurrence at 4 and 12 months Pregnancy rates at 36 months	Circular excision was quicker and had shorter haemostasis times, it had higher complete excision rates (93% vs 74.5%) Recurrence rates were not different (23.3 % with excision vs 31.% with stripping) Pregnancy rates at 36 months were not different, but the denominator for pregnancy rates is unclear, table data do not match text	Circular excision technique can be preferred to direct stripping technique	*The results of this study should be interpreted with caution*
(Porpora, *et al.*, 2010)	Prospective cohort	166 consecutive patients affected by uni- or	complete removal of ovarian endometriomas by stripping, excision of	Patient demographic characteristics, surgical	Dysmenorrhea, dyspareunia, and chronic pelvic pain recurred in	Prior surgery, presence of adhesions, and ovulation	

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
		bilateral ovarian endometrioma(s) Age 31.5 ± 6.46 9.6% had previous surgery	deep endometriosis, and coagulation of peritoneal implants with bipolar forceps. Specimens underwent thorough histologic analysis.	findings, and surgical results Pain/cyst recurrence Minimum FU: at 3-month intervals for 3 years Pain recurrence : postoperative VAS pain score of ≥5 endometrioma recurrence: presence of a cyst with a typical aspect on TVUS	14.5%, 6%, and 5.4% of women, respectively. Ovarian endometrioma recurred in 9.6% of cases.	drugs are negative prognostic factors.	
OVARIAN RESERVE							
(Muzii, *et al.*, 2016a)	RCT	51 patients with bilateral endometriomas larger than 3 cm. reproductive age with pelvic pain and/or infertility	Stripping technique and the combined excisional/ablative technique one ovary was randomized to the stripping technique and the contralateral to the combined excisional/ablative technique.	endometrioma recurrence (see above) ovarian reserve Post-operative follow-up was performed at 1, 3 and 6 months after surgery ovarian reserve : antral follicle count (AFC) and ovarian volume (ml)	ovarian reserve – AFC – 6mo Strip 4.8+2.9 Comb 4.4+2.3 P=0.57 ovarian reserve - ov vol – 6mo Strip 8.4+5.0 Comb 6.5+3.3 P=0.04 2 and 2 pregnancies occurred before the 3 and 6-month visit, resp, whereas 2 and 5 pts were started on medical treatment for pain recurrence before the 3 and 6-month visit, resp.	There is no evidence that the combined excisional/ablative technique is better than the traditional stripping technique, as similar recurrence rates were observed for the two techniques.	
(Shaltout, *et al.*, 2019)	RCT	200 women with endometrioma	• drainage • cystectomy • drainage + insertion of Surgicel inside the cyst cavity • cystectomy + insertion of Surgicel inside the remaining ovarian tissues	Recurrence (see above) ovarian reserve (AMH/AFC) FU 24 months	ovarian reserve similar impact for all techniques Drain+SURGICEL: least impact on AMH Higher decrease of AFC in drain vs Cyst+SURGICEL group (p=0.021)	Surgicel reduces effectively the recurrence risk of endometriomas and its use during laparoscopic drainage is an effective alternative for traditional laparoscopic cystectomy with minimal affection of the patient ovarian reserve.	
(Muzii, *et al.*, 2015)	Prospective controlled study	Consecutive patients with pelvic pain and/or infertility undergoing laparoscopic excision of a monolateral ovarian endometrioma for the	Second surgery for endometrioma vs first surgery	Cyst wall histologic evaluation ovarian reserve with AFC and ovarian volumes of both the operated and	 Histologic parameters of the endometrioma cyst wall. Specimen thickness and histology grade / PS group (n = 17) / RS group (n = 11) / P value Total cyst wall (mm) 1.1 ± 0.3 1.7 ± 0.3 .00003 Endometriotic tissue (mm) 0.2 ± 0.1 0.3 ± 0.1 .007 Ovarian tissue (mm) 0.3 ± 0.2 0.6 ± 0.3 .0009 Histology grade 0.4 ± 0.6 0.7 ± 0.3 .35 Note: Data are expressed as mean ± SD. PS = primary surgery; RS = recurrent surgery. AFC	Excisional surgery for recurrent endometriomas appears to be associated with histologic evidence of higher loss of ovarian tissue if compared with	

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
		first time (17 patients) or for recurrence after previous surgery (11 patients).		contralateral, non-operated ovary FU : 3 months	1st surgery; 5.1 ± 2.8 2nd surgery : 3.5 ± 1.4 P=0.07 Ovarian volume (ml) 1st surgery; 7.0 ± 2.0 2nd surgery : 5.3 ± 1.7 P=0.03	primary surgery, and may be more harmful to the ovarian reserve as evaluated by AFC.	
(Busacca, *et al.*, 2006)	Cohort study	126 Women who underwent bilateral ovarian endometrioma enucleation and younger than 40 years of age between Jan 1993 and December 2003 No comparison group	Laparoscopic bilateral endometrioma enucleation	Premature ovarian failure Follow up : 12 months or longer, Tel survey between Jan and Dec 2005	3/126 (2.4%; CI 0.5-6.8%)	Risk of ovarian failure after bilateral ovarian endometrioma cystectomy is 2.4%	Retrospective data- included as BG data, as the studies does not compare between techniques
(Younis, *et al.*, 2019)	SR	unilateral / bilateral ovarian endometrioma PubMed, EBSCO, Web of Science, ClinicalTrials.gov and the Cochrane Library, published between Jan 2000 and Oct 2018. 12 eligible STUDIES: collectively 783 women: 489 and 294 in the unilateral and bilateral groups, resp. Included studies had low risk of bias.	cystectomy.	the impact on ovarian reserve biomarkers before and after cystectomy	The pre-operative weighted mean difference (WMD) showed that serum AMH levels did not differ significantly between the groups. AMH levels were significantly (P < 0.05) lower in bilateral groups at the early, intermediate and late post-operative periods: corresponding WMDs of 0.78 ng/ml (95% CI: 0.41-1.15), 0.59 ng/ml (95% CI: 0.14-1.04) and 1.08 ng/ml (95% CI: 0.63 to 1.52), resp. (Heterogeneity was high) Pre-operative and post-operative AFC values were not significantly different between the groups. (Heterogeneity was high) Analysis of each of the unilateral and bilateral groups separately showed a significant and sustained serum AMH drop by 39.5% and 57.0%, resp from baseline to after the operation.		Only prospective controlled studies that compared the impact of unilateral versus bilateral ovarian endometriotic cystectomy on ovarian reserve tests in the same setting were included.

INCLUDED AS BACKGROUND INFORMATION
(Alborzi, *et al.*, 2004, Beretta, *et al.*, 1998)

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	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 both techniques (RCT). With regards to ovarian reserve, data show that ovarian surgery may have an impact on ovarian reserve, but there are data comparing impact of different techniques should be interpreted with caution Quality of evidence: ⊕⊕◯◯
Balance between desirable and undesirable outcomes	Surgery for improving pain, prevention of pain recurrence and disease recurrence versus the possible impact on ovarian reserve.
Balance between different outcomes	Data show benefits for cystectomy (short term data), without evidence of more harms.
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	There is no indication than one surgical technique should be preferred over the other based on resource use, equity, acceptability or feasibility, although the expertise of the clinician with either technique should be considered in decision making.
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.**

The evidence (and its quality)	For the comparison of cystectomy and laser vaporization, 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. With regards to ovarian reserve, data show that ovarian surgery may have an impact on ovarian reserve, but there are data comparing impact of different techniques should be interpreted with caution Quality of evidence: ⊕◯◯◯
Balance between desirable and undesirable outcomes	Surgery for improving pain, prevention of pain recurrence and disease recurrence versus the possible impact on ovarian reserve.
Balance between different outcomes	Data show benefits for cystectomy (short term data), without evidence of more harms.
Patient values and preference	
Resource use, equity, acceptability and feasibility	There is no indication than one surgical technique should be preferred over the other based on resource use, equity, acceptability or feasibility, although the expertise of the clinician with either technique should be considered in decision making.
RECOMMENDATION	**When performing surgery in women with ovarian endometrioma, clinicians can consider both cystectomy and 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.**

The evidence (and its quality)	With regards to ovarian reserve, data show that ovarian surgery may have an impact on ovarian reserve, but there are data comparing impact of different techniques should be interpreted with caution. Still, it was considered relevant to add a recommendations specifically addressing ovarian damage. Quality of evidence: ⊕◯◯◯
Balance between desirable and undesirable outcomes	Surgery for improving pain, prevention of pain recurrence and disease recurrence versus the possible impact on ovarian reserve (resulting in possible fertility issues).
Balance between different outcomes	Not relevant
Patient values and preference	Not relevant
Resource use, equity, acceptability and feasibility	There is no indication than one surgical technique should be preferred over the other based on resource use, equity, acceptability or feasibility, although the expertise of the clinician with either technique should be considered in decision making.
RECOMMENDATION	**When performing surgery for ovarian endometrioma, specific caution should be used to minimize ovarian damage.**

Surgery for deep endometriosis

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Arcoverde*, et al.*, 2019)	SR and MA (data for deep endometriosis only)	8 articles which included 673 patients with deep endometriosis (DE) some including bowel endometriosis and 22 articles with 1580 patients with bowel endometriosis	Laparoscopic/robotic surgery	HRQOL using SF-36, SF-12, EHP30 or EQ-5D Comparison of score pre-op versus post-op	DEEP ENDOMETRIOSIS SF-36/SF-12 (3 studies, 447 patients, pre vs post) Vitality SMD 0.67 (0.41-0.94) Social function SMD 0.59 (0.18-0.99) Role emotional 0.49 (0.02-0.97) Mental health SMD 0.39 (0.03-0.74) Physical functioning SMD 0.93 (0.48-1.38) Role physical SMD 0.45 (-0.07 – 0.97) Body pain SMD 1.23 (0.47-1.99) General health SMD 0.57 (0.02 – 1.12) MCS SMD 0.55 (0.10-1.00) PCS SMD 0.73 (0.27-1.18) The greatest improvement was observed in the Bodily Pain domain + significant improvement in MCS and PCS EHP-5 - EHP-30 (2 RCTS, n= 97): significant improvement of QOL in all domains. BFLUTS (1 study) : significant improvement in urinary HRQOL (3 mo FU) BOWEL ENDOMETRIOSIS SF-36/SF-12 (10 studies, 636 patients, pre vs post) Vitality SMD 1.00 (0.56- 1.43) Social function SMD 0.97 (0.57-1.37) Role emotional 1.17 (0.70-1.63) Mental health SMD 0.94 (0.50-1.38)	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.	

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
					Physical functioning SMD 0.74 (0.30-1.18) Role physical SMD 1.25 (0.75-1.76) Body pain SMD 1.39 (0.79-1.98) General health SMD 0.84 (0.46-1.22) MCS SMD 0.93 (0.47-1.40) PCS SMD 0.82 (0.40-1.23) The domain that had the highest improvement was Bodily Pain <u>EHP-30 and EHP-5</u> (4 studies, n=299) improvement in most domains in all studies (no meta-analysis) <u>Gastrointestinal Quality of Life Index (4 studies)</u> Not assessed, overlapping cohorts <u>BFLUTS</u> (1 study) : significant worsening in voiding symptoms but no change in storage symptoms or urinary HRQOL after surgery. <u>EQ-5D</u> (1 study, n=41) significant improvement		
(Meuleman, *et al.*, 2011b)	SR	3894 patients who underwent surgical treatment for DE with colorectal involvement	Bowel resection and anastomosis Full thickness disc resection Shave/superficial excision 32 studies; bowel resection and anastomosis only 16 studies, mixed procedures 1 study; disc resection only	Duration of follow up >24 months <24 months Number lost to follow up Number of previous therapeutic surgeries Indication for surgery Histological data Histological confirmation	Pain outcome 67%(33/49) 48% (16/33) studies 52% (17/33) studies B.Resection 53 (10.9%) Mixed 127 (20.9%) B.resection stud 59.0% Mixed stud 55.9% <u>Pain</u> B.Resection 75.2% Mixed 62.9% <u>Pain and fertility</u> B.Resection 24.8% Mixed 36.3% <u>Transmural infiltration</u> B.Res 99.2% (1067/1076)	There is a lack of consistency in the way the studies report outcome. There is a need for standardised /complete reporting in future studies	

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
			2776 (71.3%) Bowel resection and anastomosis 383 (9.8%) full thickness disc resection 679(17.4%) shaving or superficial excision 37/49 (75.5%) operations by multidisciplinary teams 24/32 B.resection 1/1 disc resection 12/16 shaving Preoperative assessment of colorectal involvement Not reported 37%(18/49) US 4% (2/49) Barium enema 26% (13/49) CT 31% (15/49) MRI 28%(14/49) Barium/CT/MRI 59%(29/49) Preop bladder/ureter assess. 10% (5/49)	Degree of infiltration Length of resection Median diameter of largest nodule Margins positive Complication rates Bowel resection studies RV fistula Leakage Abscess Postop bleeding Mixed studies RV fistula Leakage Abscess Postop bleeding Evaluation of pain Dysmenorrhoea Dyspareunia CPP QoL (pre vs postop)	Mixed 83.2%(883/1061) Serosa 94.5(121/128) Muscular 95.1% (583/613) Submucosa 37.8%(74/196) Mucosa 6.4%(17/265) 0.92-21 cm 2.9 - 4.1 cm 19.7% (25/127) 94% (46/49)studies 2.7% (55/2036) 1.5 (30/2036) 0.34% (7/2036) 3.1% (63/2036) 0.7% (12/1799) 0.7 %(12/1799) 0.3 %(6/1799) 0.3 % (6/1799) Lack of consistency Improved in most studies
				Recurrence rate	4.69-25% (10%) for studies >2 y F/U Bowel resection 5.8% Mixed 17.6% <u>In bowel resection studies</u> - suspicious recurrence: 48% (21/44) - additional surgery without endometriosis evidence: 7%(3/44) - Surgical recurrence with proven endometriosis: 45%(20/44) <u>In Mixed studies</u> - suspicious recurrence: 1% (2/138) - additional surgery without endometriosis evidence: 63%(87/138)		

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
					- Surgical recurrence with proven endometriosis: 35%(39/138)		
(De Cicco, *et al.*, 2011)	SR	1889 women who underwent segmental bowel resection for bowel endometriosis	Segmental bowel resection Studies included from January 1997 to October 2009 Follow up 2-5 years	Level of bowel resection 1096 cases Diameter of nodule 689 cases Indications for bowel surgery Duration of surgery Pain relief after surgery Recurrence of pain postop Recurrence requiring surgery Proven bowel endometriosis recurrence Spontaneous pregnancy after surgery Live birth rate after spont pregnancy Cumulative (spont + IVF) pregnancy rates Confirmation of endometriosis at histology and depth of infiltration Complication rates	Sigmoid resection 12.4%, rectum resection 87.6% 690 over 2 cm, the rest unclear Variable, some based on preop nodule size, infiltration of muscularis on MRI or US, some percentage of circumference, some decided during surgery 101-436 minutes 71.4-93.6% women pain free 1 year after surgery 23.8% (45/189, 4-54%) at 2-5 years 19.4% (61/314, 0-34%) at 2-5 years 13.9% (37/267, 0-25%) at 2-5 years 10% (2/21) and 13%(4/30) 10%(2/21), 12%(2/17), 31%(4/13) 18%(2/11), 50%(18/36), 100%(3/3) 10 articles, 527 nodules, 98% present 12 articles,612 nodules, 1% serosa, 70%muscularis, 23%submucosa, 6% mucosa 30 articles, overall 22.2% 11% major (6.4% bowel; 1.9% leakage, 1.8% fistula, 2.7% severe obstruction) 14.7 Minor (3.6% temporary bowel dysfunction, 8.1% bladder dysfunction)	Segmental bowel resection seems to be a widely acceptable option, decision to perform resection seems to be based on attitude rather than data, complication rates are similar to resections for other indications, data on sexual dysfunction lacking, in order to permit meta analysis the journals should adopt a standard way of reporting of indications, surgery, outcome, size and localisation of nodule, common use of bowel resection may be due to presence of bowel surgeons who are used to resections for cancer treatment	Complications: overall 22%, leak rate: 1.9%, overall pain relief after 1Y: 82% complete, 17% improvement, recurrence: clinical 24%, surgical 19%, endometriosis 14%

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Byrne, *et al.*, 2018a)	large cohort	5162 women of reproductive age with rectovaginal endometriosis	which 4721 women had planned laparoscopic excision, follow up 6, 12, 24 months	effectiveness (pain score, QUOL) and safety of laparoscopic surgical excision of rectovaginal endometriosis.	Menstrual pain preop 9 [9 to 9] (3857)6 month 5 [4 to 5] (1810)18 months 5 [4 to 5] (1116) 24 months - 5 [4 to 6] (524) . Deep dyspareunia 6 [5 to 6] (3987) 1 [0 to 1] (1998)1 [1 to 1] (1247)2 [1 to 2] . Cyclical dyschezia‡6 [6 to 6] (3852)1 [0 to 1] (1834)1 [0 to 1] (1157)2 [1 to 3] (536). all improvement significant to preop Global quality of life pretreatment 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.		
(Stepniewska, *et al.*, 2010)	Retrospective	n=60 segmental resection, n=40 no bowel resection, 55 DIE without bowel involvement	2000-2005, Mean F.U. 26.9 months	Pain regression if colorectal involvement, recurrence rates lower after segmental resection	The percentage of asymptomatic patients and the percentage of women who experienced an improvement was higher after bowel resection than no bowel resection. The percentage of patients who reported complete regression of pain after surgery in with and without resection were 81% and 46% for dyspareunia (P=0.002), 81% and 46% for dyschezia (P=0.010), 87% and 33% for nonmenstrual pelvic pain (P=0), and 76% and 41% for dysmenorrhea (P=0), resp. Difference in the median VAS score for all symptoms before	if colorectal endometriosis was present, postoperative pain regression was more frequent after bowel resection	

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
					and after surgery was also different between the 3 groups, with better results after bowel resection. In DIE without bowel involvement, 94% of women with dyspareunia were completely asymptomatic after surgery, 83% for dyschezia, 89% for nonmenstrual pelvic pain, and 67% for dysmenorrhea.		
(Bendifallah, *et al.*, 2020)	review and meta-analysis	endometriosis with colorectal involvement. 4 trials were included in the meta-analysis.	shaving, disc excision, and segmental resection	recurrence rate (was histologically proven recurrence 1 year after the index surgery.)	The risk of recurrence was higher after rectal shaving than after both segmental resection (OR, 5.53; 95% CI, 2.33-13.12; I(2) = 0%; p = .001) and disc excision for histologically proven recurrence (OR, 3.83; 95% CI, 1.33-11.05; I(2) = 0%; p = .01). This difference was not significant when comparing disc excision with segmental resection (OR, 2.63; 95% CI, 0.8-8.65; I(2) = 0%; p = .11).	The risk of recurrence is lower when segmental resection or disc excision is performed than when rectal shaving is performed.	

INCLUDED AS BACKGROUND INFORMATION
(Chapron, *et al.*, 2003, Kaufman, *et al.*, 2011, Wills, *et al.*, 2008)
(Angioni, *et al.*, 2015, De la Hera-Lazaro, *et al.*, 2016, Garry, *et al.*, 2000, Hong, *et al.*, 2014, Mabrouk, *et al.*, 2011, Vercellini, *et al.*, 2013)
(Bailly, *et al.*, 2013, Kent, *et al.*, 2016, Meuleman, *et al.*, 2011a, Meuleman, *et al.*, 2014)

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	Evidence of a large number of studies, not necessarily trials, is summarized in good systematic reviews. Arcoverde shows significant benefit of surgery with regards to most aspects of QoL (both in DE and bowel endo) Meuleman reported benefit with regards to pain and digestive symptoms after surgery for colorectal endometriosis. 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. This lowered the quality of evidence to low. Quality of evidence; ⊕⊕◯◯
Balance between desirable and undesirable outcomes	Benefit of surgery with regards to Qol, pain relief and pain recurrence should be weight against complications

Balance between different outcomes	Data on sexual dysfunction were lacking Meuleman (bowel endometriosis) reported a complication rate of 0–3% and recurrence rate of 5–25%; Byrne 2018 (Laparoscopic excision of deep rectovaginal endometriosis) reported an overall incidence of complications of 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. 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.
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	De Cicco concluded that DE surgery is an acceptable option. It should be considered that DE surgery is considered extensive surgery and as such is associated with significant resource use
RECOMMENDATION	**Clinicians can consider performing surgical removal of deep endometriosis, as it may reduce endometriosis-associated pain and improves quality of life.**
GPP	**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.**

Surgical approach for bowel endometriosis

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
LAPAROSCOPY VERSUS LAPAROTOMY							
(Darai, *et al.*, 2007)	cohort	71 women with bowel endometriosis Intra- and postoperative complications were evaluated, together with symptom outcomes, by means of questionnaires completed before and after surgery. mean age 33.2 ± 0.8 years 75% of the women were nulliparous. Mean BMI 22.6 ± 0.5 kg/m2. 40 (56.4%) had previously undergone surgery for endometriosis. Surgical procedures and complications were compared between the first part of the study (40 cases, previously published) and the second part (31 cases).	Laparoscopic segmental colorectal resection Of the 71 women, 64 (90%) underwent laparoscopic segmental colorectal resection, with 7 requiring laparoconversion. All the patients received GnRh analogs for 3 months before surgery. The mean follow up period after colorectal resection was 24.4 ± 2.2 months. During surgery, 62 (87.3%) were found to have complete obliteration of the pouch of Douglas. In addition to segmental colorectal resection: - cystectomy (n=23; 32.4%) - salpingo-oopho-rectomy (n=6, 8.3%) (4 bilateral + 2 unilateral) - Salpingectomy for hematosalpinx (n=5) (3 bilaterally; 2 unilaterally) - Torus resection (n= 67, 94.4%). - Uterosacral ligament resection: unilaterally (n=9; 12.7%) and bilaterally (n=53; 74.6%) Of the 71 women, 62 (87.3%) had one rectosigmoid endometriotic nodule, and 9 (12.7%) had multiple rectosigmoid lesions. - Extensive ureterolysis in 50 cases (70.4%), (24 bilaterally, 26 unilaterally) - Partial vaginal resection (n=21; 19.7%), - Hysterectomy (n= 7; 9.8%) - Appendectomy (n=2;2.8%). Other major procedures included nephrectomy (1), bladder resection (1), ureteral resection with laparoscopic reimplantation into the bladder (1), and multiple bowel	Major complications mean operating time Mean postoperative, intensity score	Major complications occurred in 9 cases (12.6%), 6 rectovaginal fistulae and 3 pelvic abscesses. mean operating time First study 6.1 h (range, 3–13 h). decreased significantly during the study (p < 0.05). 4% of the patients required blood transfusion. Mean postoperative, intensity score Dysmenorrhea 7.5 ± 2.8 1.8 ± 2.6 <0.0001, Dyspareunia 5.6 ± 3.1 1.8 ± 2.6 <0.0001, Pain at defecation 3.4 ± 2.8 1.7 ± 2.8 0.0004, Bowel movement pain or cramping 4.5 ± 3.5 1.9 ± 2.8 <0.0001, Lower back pain 4.5 ± 4.1 1.4 ± 2.7 <0.0001, Asthenia 4.8 ± 3.7 2.2 ± 3.1 <0.0001 no difference between the study periods.	This large series confirms the feasibility and efficacy of laparoscopic segmental colorectal resection. However, women must be informed of the risk for potentially severe complications.	Quantitative evaluation of gynecologic, digestive, and general symptoms before and after laparoscopic colorectal resection for endometriosis, Symptom, Mean preoperative, intensity score,

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
			resection (4). Protective colostomy (n=5; 6.9%).				
(Darai*, et al.*, 2010b)	randomized contol trial	52 patients with colorectal endometriosis to undergo laparoscopically assisted or open colorectal resection. Baseline Characteristics: Age (yr) Median 32 33.5 Range 25–44 25–44, BMI (kg/m2) Median 22.3 21.9 Range 16.4–34.6 17.2–30.5 Prior infertility, n (%) 14 (54) 9 (34.6) Duration of infertility (mo) Median 48 30 Range 24–168 24–72 Prior surgery for endometriosis, n (%) 19 (73) 16 (61.5) No. DIE lesions at preoperative MRI, n (%) Median 5 5.5 Range 3–9 2–9	laparoscopically assisted and open colorectal resections 26 patients underwent a laparoscopy and 26 open surgery "	improvement in dyschesia. improvements in other digestive and gynecologic symptoms, quality of life at least at 6 months, morbidity associated with surgery, and fertility outcomes. blood loss A 2-point improvement in dyschesia after surgery was taken to be relevant median follow-up was 19 months Conversion to open from laparoscopy, n (%) 2 (7.7) Additional DIE lesions resected, n (%) 7 (27) 8 (30.8) 0.85 Vagina 21 (80) 23 (88.5) 0.23 Uterosacral ligaments 0 3 (11.5) 0.26 Bladder 5 (19) 5 (19) 0.9 Multiple intestinal locations No. DIE lesions resected Mean 5.2 4.9 0.65 Range 3–9 0–9	improvement in symptoms significant improvement in digestive symptoms (dyschesia P<0.0001, diarrhea P < 0.01, and bowel pain and cramping P <0.0001), dysmenorrhea P < 0.0001 and dyspareunia P < 0.0001, (back pain P =[1] 0.001 and asthenia P ≤0.0001 was observed. No difference between groups Patients with complications, n (%) Overall 9 (34.6) 15 (58) 0.16 Intraoperative 3 (11.5) 5 (22) 0.7 Postoperative 8 (30.8) 14 (54) 0.16 Severity of complications, n (%) Overall 11 25 0.05 Grade 1 0 2 (8) 0.17 Grade 2 9 (81) 13 (52) 0.4 Grade 3 2 (9) 10 (40) -0.05 Total number of complications Higher in the open surgery group (P [1]= 0.04), especially grade 3 (P = 0.03). Pregnancy rate was higher in the laparoscopic group (P =[1] 0.006), cum PR was 60%. Median blood loss : lower in the lap group (P<0.05) - no difference in the nr requiring a blood transfusion Postoperative recovery : faster in the lap group; less use of parenteral morphine (P < 0.001). No difference in hospital stay Pre- and Postoperative Quantitative Questionnaires on Gynecological, : Digestive, and General Symptoms Preoperative Postoperative P Digestive symptoms (median, range) Dyschesia 4.1 (0–9) 0.7 (0–8) -0.0001 Diarrhea 2.1 (0–8) 0.6 (0–8) -0.01 Constipation 3.2 (0–10) 2.1 (0–9) 0.07 Intestinal cramps 4 (0–10) 1.4 (0–7) -0.001 Gynecologic symptoms (median, range)	Our findings support that laparoscopy is a safe option for women requiring colorectal resection for endometriosis. Moreover, laparoscopy offers a higher pregnancy rate than open surgery with similar improvements in symptoms and in quality of life.	

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
					Dysmenorrhea 7.2 (0–10) 1.8 (0–8) -0.0001 Dyspareunia 5 (0–10) 1 (0–8) -0.0001 General symptoms (median, range) Asthenia 5.4 (0–10) 2.3 (0–9) 0.001 Back pain 3.5 (0–9) 1.1 (0–9) -0.01		
(Darai*, et al.*, 2010a)	Retrospective cohort	29 women with extensive pelvic endometriosis Mean age lower in open surgery group - . BMI, parity, previous history of surgery for endo, and locations of DE were the same	radical en bloc hysterectomy and colorectal resection Open surgery (n=13), laparoscopic surgery (n=16)	Feasibility Symptoms (VAS 0-10) quality of life (SF-36 questionnaire) urinary function (International Prostate Score Symptoms (IPSS) and the Bristol Female Lower Urinary Tract Symptoms (BFLUTS) questionnaires) Mean FU: 14 months (range 1–78 months)	4 of the 16 patients (25%) required conversion to open surgery for extensive adhesions <u>Symptoms</u> significant improvement in dysmenorrhea (P<0.001), dyspareunia (P<0.001), and asthenia (P<0,001) was observed. A trend for improvement was found for diarrhea (P = 0.07) and back pain (P = 0.05), while no improvement in constipation, bowel movement pain or cramping, and dyschesia was observed. *Lap vs open:* Significant improvement in diarrhea (P<0.001) <u>quality of life</u> all the QoL items apart from physical functioning were significantly improved by surgery No difference between groups <u>urinary function</u> No difference between post and pre-op, or between groups	study demonstrates the feasibility of radical en bloc hysterectomy and colorectal resection by laparoscopy with significantly less analgesic consumption than by laparotomy. Moreover, laparoscopy offers similar improvement in gyn and digestive symptoms and in quality of life than laparotomy.	
DISCOID EXCISION							
(Ercoli*, et al.*, 2017)	Prospective	n=33 (30 analyzed), DIE rectum	Laparoscopic robotic-assisted rectal nodulectomy (LRN), 2010-2014, *mean F.U. 27.6+/-16.7 months*	Symptoms	mean VAS (0-10): dysmenorrhea 7.63 to 2.4 (p<0.01); dyspareunia 6.26 to 2.76 (p<0.01); dyschezia 4.73 to 1.1 (p<0.01); dysuria 2.06 to 0.66 (p<0.01); chronic pelvic pain 4.5 to 1.63 (p<0.01)	LRN feasible and safe	significant improvement of VAS scores
(Roman*, et al.*, 2017)	Prospective	n=111, rectal endometriosis, no comparison	Disc excision with staplers, 2009-2016, *Only 22 have >3Y F.U.*	GIQLI scores recurrence	Improvement of GIQLI scores, no data on recurrence	Disc excision valuable alternative to colorectal resection (conclusion not supported by the data)	Questionnable whether this is prospective.
(Roman*, et al.*, 2015)	Prospective	n=50, colorectal endometriosis	discoid excision 3 techniques: 20 semicircular stapled, 28 circular stapled, 2 transvaginal excision, 2009-2014, *F.U. 5-65 months*	Symptoms GIQLI	GI function, improvement of KESS, GIQLI, pain, diarrhea, constipation	Disc excision valuable alternative to colorectal resection (conclusion not supported by the data)	This study only shows that function improves after discoid excision

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Spagnolo, *et al.*, 2014)	Prospective	n=25 (36-11 lost to F.U.), Posterior DIE	Shaving/discoid excision, urodynamic/anorectal studies, 2011-2012, *median F.U. 7 months*	Symptoms urodynamic/anorectal function	Improvement of pain, but no impact on urodynamic/anorectal function	No alteration of motility/sensory capacity of bladder/rectosigmoid	No comparative study, but improvement of pain after nerve-sparing excision
SEGMENTAL RESECTION							
(Touboul, *et al.*, 2015)	RCT	n=52, colorectal endometriosis, laparoscopic vs open colorectal resection	20 lap vs 20 open, 2006-2008, at least 4Y F.U.	Symptoms	VAS dysmenorrhea 2.3 vs 2.2 (p0.9) dyspareunia 2.2 vs 2.2 (p0.96)	Symptoms/QoL improvements last over 4Y with no difference between open and lap approach, but lap has lower complications and higher pregnancy rate	
(Lyons, *et al.*, 2006)	Prospective	n=7, laparoscopic bowel resection for endometriosis, no comparison	laparoscopic endometriosis surgery, March-November 2003, VASpain after 1 year	Symptoms	median scores: Dysmenorrhea 71 to 5 (p0.028), Dyspareunia 66 to 5 (p0.08), Dyschezia 48 to 20 (p0.173)	Improvement of pain and QoL	Only few patients
(Garavaglia, *et al.*, 2018)	cohort	n=20, intestinal endometriosis,	laparoscopic colorectal resection, 2010-2015, F.U. 52 months (16-72)	Symptoms SF-36 QoL	SF-36 QoL, improvement of dysmenorrhea (p=0.00001), pelvic pain (p=0.001), rectorrhagia (p=0.02), constipation (p=0.04)	Positive impact of laparoscopic resection on QoL	no comparison of techniques
(Riiskjaer, *et al.*, 2018)	Prospective	n=175, Rectosigmoid endometriosis	Laparoscopic bowel resection, no comparison, but before-after study, 2011-2015, F.U. @1y (97% respons rate)	Symptoms SF-36 QoL	Pain and QoL. Decrease in pain parameters (p=0.0001), improvement of QoL SF36 (p=0.0001)	Significant and clinically relevant improvement @1Y after resection; strong recommendation for surgery	
(Kent, *et al.*, 2016)	Prospective	n=137, but 100 FU of 12 months, before-after design	Surgery for bowel endometriosis	EHP30 questionnaire GIQLI VAS for chronic pelvic pain, dyspareunia, dysmenorrhea, and dyschezia	serious perioperative and postoperative complication rate was 7.3% Significant improvement in almost all variables studied	Pelvic clearance of endometriosis improves outcome regarding pain, sexual function, and QoL	
(Ruffo, *et al.*, 2014)	Retrospective	n=900, laparoscopic bowel resection	Segmental resection, 2002-2010, F.U. 54 (1-120)	diarrhea, constipation, rectal bleeding, tenesmus, dyschezia, dysuria, dyspareunia, fertility, recurrence	All the evaluated symptoms significantly improved over time, with P = 0.0001 for dyspareunia, constipation, and pelvic pain and P = 0.004 for diarrhea. Nonsignificant improvement was reported for dysuria and rectal bleeding (with P = 0.452 and P = 0.097, resp.).	Symptoms significantly improve over time	no comparison
(Silveira da Cunha Araujo, *et al.*, 2014)	Prospective	n=45, DIE with colorectal resection, no comparison	laparoscopic resection, 2007-2012, F.U. 48 months (36/45 pts)	QoL SF36	QoL SF36, Bodily pain 25.83 to 64.11 (p<0.001)	Improvement of long-term QoL	no comparative study, but improvement of pain
(Ribeiro, *et al.*, 2014)	Prospective	n=45, Intestinal endometriosis, no comparison of technique	laparoscopic colorectal resection, 2007-2008, F.U. 1year	QoL SF36	QoL SF36, Bodily pain 21 to 82 (p<0.0001)	Improvement of QoL @ 1 year	no comparative study, but improvement of pain
(Roman, *et al.*, 2013)	Retrospective	n=75, DIE rectum, before-after design	Radical approach 24 and symptom-guided approach 51, 2005-2010, median FU unclear	KESS, GIQLI, and FIQL scores	Improvement of KESS, GIQLI, and FIQL scores on almost all domains	Support of a conservative approach	
(Mabrouk, *et al.*, 2012)	Prospective	n=47, symptomatic colorectal endometriosis	laparoscopic segmental resection, 2008-2010, F.U. 18 (6-35) months	Symptoms QoL SF36	QoL SF36,mean PCS pre 42 post 68, MCS pre 41 post 66, VAS: defaction pain 8 to 0 (p<0.0001), dyspareunia 5 to 0 (p<0.0001), chronic pelvic pain 2 to 0 (p<0.0001), Dysmenorrhoea 8 to 0 (p<0.0001)	Significant improvement of pain, no impact on satellite lesions or positive margins	

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Bassi, *et al.*, 2011)	Prospective	n=151, DIE	laparoscopic segmental resection, 2002-2009, F.U.@1Y	VAS pain scores, QoL SF36	Significant improvement in almost all variables (VAS pain scores, QoL SF36)	Improvement of patients' QoL after laparoscopic segmental resection	
(Meuleman, *et al.*, 2011a)	Retrospective	n=45, DIE with colorectal invasion, no comparison, but before-after study	Laparoscopic colorectal resection, 2004-2006, Median F.U. 27 (16-40) months	VAS pain scores surgical recurrence rate histological recurrence	Significant improvement of Vas pain scores: chronic pelvic pain 61 to 2 (p<0.0001), dysmenorrhea 92 to 13.5(p<0.0001), dyspareunia 28 to 1(p<0.0001), surgical recurrence rate 11%, histological recurrence 4%	Laser laparoscopy and bowel resection improves pain, sexual function and QoL	
CONSERVATIVE SURGERY (SHAVING AND/OR DISCOID EXCISION) COMPARED TO SEGMENTAL RESECTION							
(Roman, *et al.*, 2018)	RCT	n=60, rectal endometriosis up to 15 cm, conservative versus radical surgery	27 conservative vs 33 resection, 2011-2013, F.U. 24 months	Proportion of patients with 1 of following symptoms: constipation, frequent bowel movements, defecation pain, anal incontinence, dysuria or bladder atony.	primary outcome: 48.1 vs 39.4%, OR=0.70, CI 0.22-2.21 temporary stoma rate is high in both groups (59 and 64%)	Conservative surgery is feasible, no significant superiority for functional digestive or urinary symptoms	This is the only RCT available comparing 2 techniques.
(Bourdel, *et al.*, 2018)	Retrospective	n=195, rectovaginal endometriosis(>2 cm)	172 shaving and 23 colorectal resection, 2000-2013, Mean F.U. 60+/-42 months(shaving) and 67+/-47 months(resection)	VAS score QoL	Mean VAS score shaving:5.5 to 2.3 (p<0.001) and resection:7.3 to 2(p<0.001), significant improvement of dysmenorrhea, no differences in QoL	Whenever possible, shaving has equal impact on pain and pregnancy rates compared to resection	
(Bafort, *et al.*, 2020b)	Single-center retrospective study	232 women undergoing surgery for deep endometriosis infiltrating the rectum up to 15 cm from the anus with at least involvement of the muscularis layer (rectal endometriosis) Subgroup analysis was performed in patients without previous therapeutic laparoscopy for endometriosis (n = 108).	conservative surgery and segmental resection All patients underwent CO2-laser laparoscopic surgery: 61 underwent conservative surgery, and 171 had a segmental resection.	Postoperative complication rate (Clavien-Dindo classification).	Clavien-Dindo type 1 and 2 complications did not differ between both groups. Clavien-Dindo type 3 complications were more frequent in the segmental resection group (1/61 [1.6%] conservative vs. 18/171 [10.5%] segmental), after propensity analysis only a trend was retained. In the subgroup analysis, no difference or trend was found (1/27 [3.7%] conservative vs. 5/81 [6.2%] segmental). A low rate of temporary diverting stoma was recorded: 24/232 (10.3%).	A higher major complication (Clavien-Dindo >/=3) rate for segmental resections compared with conservative surgical treatment was shown in the overall population, although after correction for group differences this was attenuated to a trend only. However, in patients without previous therapeutic laparoscopy no significant difference or trend was found regardless of the surgical technique used. This not only suggests that redo/repeated surgery has a potentially increased morbidity, but also emphasizes the importance of a well executed primary surgery.	
DISCOID EXCISION COMPARED TO SEGMENTAL RESECTION							
(Hudelist, *et al.*, 2018a)	Prospective	n=134, DE rectosigmoid up to 25cm, 112 (83.6%) women were followed up long-term.	102 segmental resection vs 32 disk excision, 5 year, 36.5 months vs 34.3 months	reduction in pain symptoms fertility outcomes complication rates according to Clavien-Dindo class	no difference in duration of surgery, complication rates, mean hospital stay, or discrepancy in hemoglobin level. Significant decrease in pain symptoms and increase in quality of life scores. No significant difference regarding reduction of pain	Both techniques reduce pain, improve fertility, with equal morbidity	No direct comparison, but before-after study, >90% would repeat surgery

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
					symptoms, fertility, and functional outcomes between group. Of all the 61 infertile women, 26 (42.6%) became pregnant spontaneously, and 13 (21.3%) by IVF with an overall pregnancy rate of 63.4%. The overall complication rate (Clavien-Dindo III-IV) was 8 of 134 (5.9%) without statistically significant difference between the cohorts.		
(Roman, *et al.*, 2010)	Retrospective	n=41 Women who had undergone surgical management of rectal endometriosis with at least 1 year of post-operative follow-up	rectal endometriosis, resection (n= 25), nodule excision (n=16) 2005-2008, Mean F.U. 26(12-53)months	Post-operative symptoms	An increase in the number of daily stools ≥3 was observed in 13 (52%) segm vs 3 (19%) nodule group (P = 0.02). Severe constipation (<1 stool/5 days) was recorded in 3 women in segm group. The probabilities of being free of dysmenorrhea, dyspareunia and non-cyclic pain at 24 mo segm : 80% (95% CI: 55–92%) 65% (95% CI: 42–81%), 43% (95% CI: 23–62%) NOD: 62% (95%CI: 34–81%), 81% (95% CI: 52–94), 69% (95% CI: 40–86%). Significantly lower post-operative score for pain in both groups. No significant difference in pain improvement between groups	colorectal segmental resection associated with worse functional outcome, no differences in pain improvement	
(Fanfani, *et al.*, 2010)	case-control study	136 deep infiltrating and intestinal endometriosis	discoid resection (n=48) vs segmental resection (n=88) 2003-2007 median FU 33 vs 30 months	short- and long-term outcome Operative data Complications	Operating time 100 min (120-480) vs 300 min (90-540 (p=0.02) Temporary ileostomy 1/48 (2.1%) vs 8/88 (9.1%) (p=0.04) No diff in estimated blood loss, Hospital stay, Laparotomic conversion Fever 1/48 (2.1%) vs 11/88 (12.5%) (p=0.04) Severe rectal bleeding 4/48 (8.4%) vs 0 (p=0.037) Urinary retention after 30 d 0 /48 vs 13/88 (14.7%) (p=0.04)	Discoid resection with stapler is feasible with improvement of endometriosis-related symptoms	questionable patient selection

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
					No diff in blodd transfusion, pelvic abcess, reinterventions,or other complications Subjective satisfaction 93.0% vs. 88.8% (no diff), recurrence rate 13.8% vs. 11.5% (no diff),		
SHAVING VS DISCOID EXCISION VS SEGMENTAL RESECTION							
(Abo, *et al.*, 2018)	Retrospective	n=364 consecutive women with bowel endometriosis	Shaving (n=145), disc excision (n=80), or segmental resection (n=139)	postoperative complications (fertility data)	Clavien 3b postoperative complications were recorded in 43 patients (11.8%), two thirds of whom were managed by segmental colorectal resection (P<.001). 14 rectovaginal fistula (3.8%) were reported: 3 shaving (2.1%), 3 disc excision(3.7%), and 8 segmentall resection arm (5.8%) (P=0.13). 24 (6.6%) of pelvic abscess in patients free of fistula or leakage.	Whenever possible, shaving should be performed	no data on pain/recurrence . Postop outcome only, comparing 3 techniques
(Mabrouk, *et al.*, 2018)	cohort	n=392, rectosigmoid endometriosis, no comparison	shaving(SG) 76%, disc excision(DG) 8%, resection(RG) 16%, 2004-2017, F.U. 43months (12-163)	Complications Recurrence rate	Complications: SG 5.4%, DG 9.1%, RG 17.7% p=0.004, Recurrence rate (proven): SG 4%, DG 3%, RG 0% NS	Conservative surgery is preferred, similar recurrence rates and fewer short-term complications	retrospective data, rather small groups
(Afors, *et al.*, 2016)	Retrospective	n= 92, bowel endometriosis	3 groups: shaving 47, discoid excision 15, segmental resection 30, 2010-2012, >24 months F.U.	Symptoms re-intervention rate	Shaving has higher recurrent dysmenorrhea/dyspareunia and higher re-intervention rate	Nodule>3cm RR2.5 of requiring bowel resection, avoid shaving in big nodules	

Complications of surgery for bowel endometriosis

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Kondo, *et al.*, 2011)	retrospective cohort	568 women from a database who had laparosopcy for DIE	laparosopcy for DIE	Complications after surgery for deep endometriosis	Intraoperative complications occurred in 12 women (2.1%), including 6 minor (1.05%) and 6 major (1.05%) complications. Postoperative complications developed in 79 women (13.9%), including 54 minor (9.5%) and 26 major (4.6%) complications (one woman had both minor and	surgery for deep endometriosis is feasible, but it is associated with major complications, especially when any type of rectal surgery must be performed.	

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
					major postoperative complications). The overall major postoperative complication rate for women who underwent any type of rectal surgery (shaving, excision and suture, or segmental resection) was 9.3% (21 out of 226), compared with only 1.5% for the other women (five out of 342) (P < .01). Shaving presented less major postoperative complications compared with segmental resection (24 versus 6.7%; P = 0.004).		
(Donnez and Squifflet, 2010)	prospective series	500 deep rectovaginal endometriotic nodules	shaving technique	Complication rates recurrence rates (Pregnancy rates) The median follow-up duration was 3.1 years (range 2–6 years).	Major complications included: (i) rectal perforation in 7 cases (1.4%); (ii) ureteral injury in 4 cases (0.8%); (iii) blood loss .300 ml in 1 case (0.2%); and (iv) urinary retention in 4 cases (0.8%). The recurrence rate was 8%	In young women, conservative surgery using the shaving technique preserves organs, nerves and the vascular blood supply, yielding a high pregnancy rate and low complication and recurrence rates. There is a need, however, for further strong and energetic debate to weigh up the benefits of shaving (debulking surgery) versus rectal resection (radical surgery)	
(Meuleman, *et al.*, 2011b)	Study details outlined above						
(De Cicco, *et al.*, 2011)	Study details outlined above						

Surgery for posterior compartment endometriosis excluding bowel endometriosis

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
ENDOMETRIOSIS OF THE UTEROSACRAL LIGAMENTS AND VAGINA							
(Chapron and Dubuisson, 1996)	case series	21 patients treated by laparoscopic surgery between January 1993 and June 1994 for USL endometriosis	Laparosocpic resection of all the uterosacral ligament(s) presenting deep endometriotic lesions together with exercise of all other endometriotic lesions. Follow up minimum 12 months.	no intraopertaive complications. The efficiency of the treatment emasured by pre and postop pain outcomes.	Patients with dysmenorrhoea (19 cases) improved in 84.2% of cases (16 patients). 17 patients with deep dyspareunia, improvement was evident for 94.1% of cases (16 patients). CPP improved in seven out of nine cases (77.7%).	These results demonstrate that, provided the surgeon is highly skilled in laparoscopy, laparoscopic surgery is efficient for the treatment of patients presenting painful symptoms related to deep endometriotic implants located on the uterosacral ligaments.	
(Angioli, *et al.*, 2014)	prospective case series	34 women operated for symptomatic deep recto-vaginal endometriosis with full thickness vaginal wall involvement	systematic surgical approach combining vaginal and laparoscopic steps for patients affected by deep endometriosis infiltrating the vaginal wall, follow up at 3, 6, 12 and 24 months	two years' follow-up with pelvic examination, transvaginal ultrasound and visual analog scale (VAS) evaluation of symptoms (dysmenorrhea, dyspareunia and chronic pelvic pain) at 3, 6, 12 and 24 months	No major complications were registered. Complications included superficial vascular lesions 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)	The proposed systematic surgical approach consisting of three consecutive steps could simplify the approach to deep endometriosis while at the same time increasing the quality of endometriosis surgery, with important benefit for the women affected.	
ENDOMETRIOSIS OF THE CUL-DE-SAC							
(Reich, *et al.*, 1991)	retrospective case series	100 women with endometriosis and cul-de-sac obliteration secondary to retrocervical deep fibrotic endometriosis (48 partial, 52 complete). Indications for laparosocpy - infertility (46 cases), pain (46), hypermenorrhea (7) and a mass (1).	Laparoscopic aqua-dissection, electrosurgery, CO2 laser, scissors, probes to identify the upper posterior vagina and rectum, and multiple rectovaginal examinations. In all the procedures the anterior rectum was freed to the loose areolar tissue of the rectovaginal septum prior to excising deep fibrotic endometriosis.	not stated	Laparoscopic cul-de-sac dissection, though time intensive, offers increased fertility potential and significant symptom relief.		
(Hong, *et al.*, 2014)	comparative case series	390 patients with pathologically proven DE in the cul-de-sac who	laparosocpic surgery for DIE , outcomes compared for women with and without hysterectomy	Complications, preoperative and postoperative visual analog scale (VAS)	In the hysterectomy group, perioperative complications occurred in 5 patients (6.6%), including moderate hydronephrosis	Laparoscopic radical excision of DE in the cul-de-sac is safe and significantly improves	

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
		underwent laparoscopic surgery		pain scores and HRQOL data from the 36-item Short Form (SF-36) questionnaire	(n=1) that required postoperative double-J catheterinsertion, pelvic abscess (n=1), vaginal stump suture sitebleeding (n=2), and bowel leakage that required reoperation(n=1). In the nonhysterectomy group, there were no severeperioperative complications, and perioperative complica-tions occurred in 10 patients (3.1%), including mild hydro-nephrosis (n=1), rectal serosal injuries that were repairedintraoperatively (n=2), pelvic abscess (n=2), postoperativefever (n=2), vaginal wall suture site disruption (n=1), sig-nificant intraoperative venous bleeding that was controlled bycoagulation (n=1), and significant intraoperative arterialbleeding (caused by injury to the left internal iliac artery) thatwas controlled by coagulation (n=1). SF 36 is recoreded in tables and graphs - no pre and postop pain scores reported	HRQOL, especially in terms of pain. The severity of endometriosis may affect the degree of improvement in HRQOL scores.	
ENDOMETRIOSIS OF THE BLADDER AND URETERS							
(Goncalves, *et al.*, 2019)	Retrospectiv e cohort	10 patients with bladder endometriosis (BE)	surgical treatment: - 2 laparoscopic shaving of the bladder lesion - 8 laparoscopic partial cystectomy. Simultaneous resection of coexisting pelvic nodules	Pre- and postoperative data, intraoperative findings, type of surgical procedure, and intra- and postoperative complications	No conversions to laparotomy Complications: - Intraoperative (n=1): - major or minor postoperative complications (n=0) Repeated interventions (n=0) clinical symptoms - Improvements were reported - increase in long-term urinary frequency after surgery (n=0) - urinary symptom recurrence (n=1)	Laparoscopic partial cystectomy and shaving of the bladder lesion seem to improve urinary symptoms, with a low rate of intra- and postoperative complications and a low rate of recurrence, without affecting long-term bladder capacity	
(Chapron, *et al.*, 2010)	Cohort study	75 consecutive patients with histologically proved bladder DE - isolated bladder DE (Group A) - associated symptomatic posterior DE (Group B)	partial cystectomy + Complete surgical exeresis of all associated symptomatic DE lesions	rate of recurrence (i.e. clinical reappearance of the disease or radiological evidence that mandated a new surgical procedure)	bladder DE recurrence: none Pain symptoms: - significant improvement - 2 patients (2.7%) developed major complications during follow-up.	No patients required further surgery for bladder recurrence after radical surgery consisting in partial cystectomy. Exeresis of associated posterior DE nodules is	

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
		- associated asymptomatic posterior DE (Group C) mean follow-up 50.9 +/- 44.6 months		pelvic pain symptoms pre- and post-operatively using a 10-cm VAS outline the surgical modalities for handling associated posterior DIE nodules	Among patients with non-operated associated asymptomatic posterior DE lesions (n = 15), a second surgical procedure indicated for pain symptoms was necessary in only one patient (6.7%).	indicated only when they are symptomatic.	
(Pontis, *et al.*, 2016)	prospective observational study	16 women with symptomatic bladder endometriosis	bladder nodule was excised with a transurethral and laparoscopic combined approach technique Operative time was 120.18 +/- 15.77 minutes and mean blood loss was 65.12 +/- 44.74.	pre-surgical and post-surgical outcomes Intensity of lower urinary tract symptoms (VAS score) (pre-op and post-op – 1,6 and 12 months) quality of life (SF-36) and sexual functions (FSFI) (pre-op and 12 mo post-op)	No intraoperative and postoperative complications, nor conversion laparotomy Intensity of lower urinary tract symptoms were significantly lower after 1, 6 and 12 months postsurgery vs. presurgery ($p < 0.001$). significant improvement in the quality of life and sexual functions	This surgical approach is safe and simple in the treatment of bladder endometriosis, with low risks and optimal resolution of symptoms, and improvement of quality of life and sexual function.	
(Kovoor, *et al.*, 2010)	Retrospective study	deep bladder endometriosis. - 21 consecutive patients with endometriotic nodule on the bladder (infiltrating detrusor muscle) Median FU 20 months. 16 patients (76%) had associated deep lesions in the pelvis; rectovaginal nodules (38%), ureteric lesions (14%), with signs of obstruction.	laparoscopic excision No conversion 10 patients (47.6%) partial cystectomy, 11 partial-thickness excision of the detrusor muscle.	primary outcome : resolution of bladder symptoms. Secondary outcomes: complication rates, recurrence rates, and pregnancy rates after laparoscopic surgery.	Major complications developed in 3 patients (14%), primarily related to bowel resection. 6 patients became pregnant (60%). No disease recurrence.	Laparoscopic excision is feasible in all types of bladder endometriosis but often involves multiple procedures to manage associated lesions, especially rectovaginal nodules and ureteric lesions. Complications are primarily related to severity of the disease and associated procedures.	
(Schonman, *et al.*, 2013)	Retrospective review of medical records	69 patients with bladder endometriosis Mean age 31.3 +/- 4.6 years. Preoperative urinary symptoms (such as frequency, urgency, dysuria and others) were present in 28 (40.0%) patients. median (range) follow-up: 60 (4-92) months	laparoscopic treatment	Efficacy, safety and long-term outcome pre-, intra- and postoperative information	Deep detrusor involvement in 45 (65.2%) patients. Of these, 21 patients underwent partial cystectomy due to a full thickness lesion. Deep nodule resection without bladder invasion was performed in 24 (34.8%) patients and bladder nodule coagulation and ablation in the remaining 24 (34.8%) patients with superficial involvement.	After a long-term follow-up surgical management of bladder endometriosis is strongly recommended. During surgery, careful inspection and full excision of bladder lesions should be performed. Laparoscopic excision is a safe and efficacies approach.	

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
					No intraoperative complications. Postoperative follow-up results were available for all patients. After FU, 92.7% of the patients were asymptomatic or reported improvement in symptoms.		
(Cavaco-Gomes, *et al.*, 2017)	review	ureteral endometriosis (UE) 18 articles were included, including a total of 700 patients with ureteral endometriosis. 57% of patients had at least one previous surgery for endometriosis. Preoperative evidence of significant hydroureter/hydronephrosis was found in 324 of 671 (48.3%) patients. Dysmenorrhea (81.4%), pelvic pain (70.2%) and dyspareunia (66.4%) were the presenting symptoms more commonly reported by the patients. Most patients presented no symptoms specific to the urinary tract.	Laparoscopy	including preoperative evaluation, surgical details and postoperative follow-up.	Ureteral endometriosis was more frequent in the left ureter (53.6%) and it was bilateral in 10.6% of cases. Ureterolysis alone was considered a sufficient procedure in 579 of 668 patients (86.7%), and in the remaining 89 patients ureteral resection was necessary. Rectovaginal and uterosacral involvement was present in 58.8% and 47.9% of patients, respectively. Concomitant ureteral and bladder endometriosis in 19.8%. Accidental ureteral injuries in 1-24% of patients (6 studies). Conversion to laparotomy in 3-6,7% of patients. (6 studies). Major postoperative complications : 21 / 682 patients (3.2%). The need for reoperation during follow-up period because of ureteral endometriosis persistence or recurrence : 3.9%.	When performed in specialized centers, laparoscopic ureterolysis showed to be a feasible and safe procedure, with a low risk of complications and with satisfactory long-term results. This conservative approach may be used as the initial treatment option in most patients with ureteral endometriosis.	
(Hudelist, *et al.*, 2018b)	Retrospective cohort study	207 patients with DE, 50 exhibited urinary tract endometriosis, comprising 30 patients with bladder endometriosis and 23 women with solitary or additional hydronephrosis. median follow up of 23 months	preoperative transvaginal sonography (TVUS) Surgery: laparoscopic partial cystectomy and/or ureterolysis/decompression, ureteric resection and end-to-end anastomosis or ureteroneocystostomy for ureteral stenosis and hydronephrosis.	Accuracy surgical outcomes regarding fertility and pain symptoms	Sensitivity, specificity, positive and negative predictive value, positive/negative likelihood ratios and test accuracy for TVUS detecting bladder endometriosis were 93%, 99%, 97%, 99%, 155.5, 0.07 and 98.6% resp. Surgical outcomes: - Duration of surgery : 205 min (range 89-365 min), - average blood loss was 1.6 g/dL (range 0.3-4.6 g/dL)	Laparoscopic surgery for urinary tract endometriosis is effective for treatment of hydronephrosis, reduction of pain symptoms and may improve fertility. Transvaginal sonography is highly accurate for presurgical detection of bladder involvement.	

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
					- hospital stay : average 8 days (range 2-16 days). - Conversion rate : 4%. - Grade III complications: 5 - Symptoms: a decrease in dysmenorrhea (7.6-1.6; p < 0.001), dyspareunia (3.0-0.9, p < 0.001) and dysuria (3.3-0.2; p < 0.003), and an increase in quality of life (3.3-8.1; p < 0.001). Overall clinical pregnancy rate was 46% and life birth rate 18%.		

Nerve-sparing laparoscopy

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(de Resende, *et al.*, 2017)	SR of randomized clinical trials, intervention or observational (cohort and case-control) studies	4 studies of women who underwent surgery for painful DIE.	nerve sparing versus non nerve sparing techniques	urinary retention, need to self catheterise at discharge and at 90 days postop	RR of 0.19 [95%CI: 0.03-1.17; (I(2) = 50.20%; P = 0.09)] for need of self-catheterization at discharge in the NS group in relation to the conventional technique. Based on two studies, common RR for persistent urinary retention (after 90 days) was 0.16 [95%CI: 0.03-0.84].	Controlled studies evaluating the best approach to manage the urinary tract after complex surgery for DIE are needed	
(Uccella, *et al.*, 2018)	prospective case series	34 women operated for DIE of the posterior compartment 28 (82.4%) had already undergone a previous abdominal surgery for endometriosis.	laparoscopic excision using a nerve-sparing technique, data collected before surgery and 6 and 12 months after surgery Bowel resection was performed in 16 (47.1%) patients.	(VAS pain scores before surgery and 6 and 12 months. Bladder, rectal, and sexual function, were evaluated using validated questionnaires (i.e., ICIQ-UISF, NBD score, and FSFI) pre-operatively and 6 months after .	Median VAS score levels of pelvic pain were significantly decreased after surgery both at 6 (median 3, range 0-7 and 2, 0-7, resp) and at 12 months (3, 0-8 and 2, 0-7), compared to pre-operative levels (9, 1-10 and 3, 0-7, resp) (p<0.0001). No differences were found in terms of urinary function between pre- and post-operative ICIQ-SF questionnaires. In no cases, bladder self-catheterization was needed at the 6-and 12-month follow-up. Median NBD score was 3.5 (0-21) pre-operatively and 2 (0-18) after 6 months (p = 0.72). The pre-operative total FSFI score was 19.1 (1.2-28.9) vs. 22.7 (12.2-31) post-operatively (p = 0.004)	The nerve-sparing approach is effective in eradicating DIE of the posterior compartment, with satisfactory pain control, significant improvement of sexual function, and preservation of bladder and rectal function.	

EVIDENCE TO RECOMMENDATIONS

No recommendation: 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.

Hysterectomy for endometriosis-associated pain

Summary of Findings Table

Not feasible based on the retrieved data

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Namnoum, *et al.*, 1995)	Historical prospective study	138 women with endometriosis	hysterectomy with or without ovarian preservation 29 Hx with some ovarian tissue preserved; 109 had HX+BSO 1979 to 1991	recurrence and/or reoperation Follow-up information was obtained from medical records, outpatient charts, and telephone surveys	Hx only 18/29 (62%) recurrent pain 9/29 (31%) required reoperation. Hx+BSO 11/109 (10%) had recurrent symptoms 4/109 (3.7%) required reoperation. Ovarian conservation was associated with a RR for pain recurrence of 6.1 (95%CI 2.5 to 14.6) compared with patients with oophorectomy. The RR for reoperation was 8.1 (95% CI 2.1 to 31.3).	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	
(Shakiba, *et al.*, 2008)	retrospective study	240 surgery for endometriosis-associated pain	hysterectomy with or without oophorectomy (n=120) OR laparoscopic excision of endometriotic lesions (n=120) Estimates of reoperation-free survival at 2, 5, and 7 years (Kaplan-Meier methods/ hazard ratios	Estimates of reoperation-free survival at 2, 5, and 7 years (Kaplan-Meier methods/ hazard ratios	surgery-free percentages (2/5/7yrs) exc : 79.4%, 53.3%, 44.6%, HX-only: 95.7%, 86.6%, 77.0% HX+BSO: 96.0%, 91.7%, 91.7% Local excision had a 4 times higher failure risk than HX-only (P=.003). in women between 30 and 39 years of age, removal of the ovaries did not significantly improve the surgery-free time.	Local excision of endometriosis is associated with good short-term outcomes but, on long-term follow-up, has a high reoperation rate. Hysterectomy is associated with a low reoperation rate. Preservation of the ovaries at the time of hysterectomy remains a viable option.	

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Sandström, *et al.*, 2020)	population-based registry study.	137 Women aged 18–45 years - hysterectomy for endometriosis between 2010 and 2015.	hysterectomy	Pelvic or lower abdominal pain after Hx	Proportion experiencing pain of any severity decreased by 28% after Hx ($p < 0.001$). Proportion of women with severe pain symptoms decreased by 76% after Hx ($P<0.001$). Satisfaction : 84% Presence of severe pain symptoms after the HX was associated with less satisfaction ($P < 0.001$). Pain symptoms after surgery, patient satisfaction and the patient's perceived improvement were not significantly different between women whose ovarian tissue was preserved and women who underwent BSO	significant, long-lasting reduction in pain symptoms after HX	

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	HX seems to have good outcomes with regards to (long term) pain relief and long term prevention of re-operation. Quality of evidence: ⊕⊕◯◯ Hysterectomy with bilateral salpingo-oophorectomy may have a significant long-term impact and may create a need for hormone replacement therapy. 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 within the retained cervix and/or adjacent to it with subtotal hysterectomy.
Balance between desirable and undesirable outcomes	The benefit of HX+BSO on pain symptoms needs to be balanced against the impact for fertility (although ovarian tissue preservation did not impact on outcomes)
Balance between different outcomes	In general, the benefits do not outweigh the risks (sequelae), and conservative approaches are preferred. For specific subgroups (those women who no longer wish to conceive and failed to respond to more conservative treatments) benefits could outweigh the risks and Hx can be considered
Patient values and preference	It should be considered that hysterectomy, especially when combined with bilateral salpingo-oophorectomy, is not an option for women still wishing to conceive. Additionally,
Resource use, equity, acceptability and feasibility	

RECOMMENDATION	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.
GPP	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.

QUESTION II.3B IS THERE A SUBGROUP OF WOMEN WITH CONFIRMED ENDOMETRIOSIS WHO RESPOND BETTER TO SURGERY THAN OTHERS?

NARRATIVE QUESTION

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Not applicable

INCLUDED REFERENCES FOR NARRATIVE DISCUSSION
(Abbott*, et al.*, 2003, Ball*, et al.*, 2021, Banerjee*, et al.*, 2006, Chopin*, et al.*, 2005, Ghai*, et al.*, 2020, Milingos*, et al.*, 2006)

EVIDENCE TO RECOMMENDATIONS

Not applicable

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.

The following research recommendation was formulated: “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.”

QUESTION II.4 ARE MEDICAL THERAPIES EFFECTIVE AS AN ADJUNCT TO SURGICAL THERAPY?

Preoperative medical treatment

Summary of Findings Table

QII.4a Presurgical medical therapy compared to placebo or no medical therapy for improving surgical outcomes in endometriosis

Patient or population: improving surgical outcomes in endometriosis
Intervention: presurgical medical therapy
Comparison: placebo or no medical therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no medical therapy	Risk with presurgical medical therapy				
Pain recurrence follow up: 12 months	241 per 1,000	**265 per 1,000** (173 to 400)	**RR 1.10** (0.72 to 1.66)	262 (1 RCT)	⨁⨁◯◯ LOW [a,b]	No benefit for presurgical therapy
Dysmenorrhea recurrence follow up: 12 months	197 per 1,000	**280 per 1,000** (181 to 436)	**RR 1.42** (0.92 to 2.21)	262 (1 RCT)	⨁⨁◯◯ LOW [a,b]	No benefit for presurgical therapy
AFS score at 3 months (for assessing Disease recurrence)	The mean AFS score at 3 months (for assessing Disease recurrence) was **44.1**	MD **9.6 lower** (11.42 lower to 7.78 lower)	-	80 (1 RCT)	⨁⨁◯◯ LOW [a,c]	

Explanations
a. Single study
b. Imprecision detected
c. AFS score for disease recurrence

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Chen, *et al.*, 2020)	Cochrane review	Endometriosis	presurgical medical therapy versus placebo or no medical therapy	Pain Pain recurrence Disease recurrence	See SOF table QII.3 A	uncertain if presurgical medical hormonal suppression reduces pain / disease recurrence at 12 months or less	

INCLUDED AS BACKGROUND INFORMATION
(Furness, et al., 2004)

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	Cochrane review shows no benefit of presurgical medical therapy for reducing pain / disease recurrence after endometriosis surgery. There are no controlled studies supporting the use of pre-operative medical treatment to facilitate surgery or improve the outcome of surgery Quality of evidence: ⊕⊕◯◯
Balance between desirable and undesirable outcomes	Benefit with regards to pain management versus side-effects related to medical treatment
Balance between different outcomes	No evidence of benefit – no benefit of harm (ie can be used for pain management prior to scheduled surgery)
Patient values and preference	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
Resource use, equity, acceptability and feasibility	The guideline group confirms the recommendation from the previous ESHRE guideline (Dunselman*, et al.*, 2014). 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.
RECOMMENDATION	**It is not recommended to prescribe preoperative hormone treatment to improve the immediate outcome of surgery for pain in women with endometriosis.**

Postsurgical medical therapy for improving surgical outcomes (short term disease and pain recurrence)

Summary of Findings Table

QII.4b Postsurgical medical therapy compared to placebo or no medical therapy for improving surgical outcomes in endometriosis

Patient or population: improving surgical outcomes in endometriosis
Setting:
Intervention: postsurgical medical therapy
Comparison: placebo or no medical therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no medical therapy	Risk with postsurgical medical therapy				
Pain recurrence follow up: up to 12 months	255 per 1,000	**178 per 1,000** (132 to 239)	**RR 0.70** (0.52 to 0.94)	657 (5 RCTs)	⨁⨁◯◯ LOW [a,b]	Favours postsurgical medical therapy
Disease recurrence follow up: up to 12 months	171 per 1,000	**51 per 1,000** (29 to 92)	**RR 0.30** (0.17 to 0.54)	433 (4 RCTs)	⨁⨁◯◯ LOW [a,b]	Favours postsurgical medical therapy

Explanations
a. Direction of the effect is not consistent across studies
b. Imprecision detected

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Chen, *et al.*, 2020)	Cochrane review	Endometriosis	postsurgical medical therapy versus placebo or no medical therapy	Pain Pain recurrence Disease recurrence	See SOF table QII.3 B	postsurgical medical therapy - may decrease pain recurrence at 12 months or less - uncertain if improves disease recurrence at 12 months (AFS score) - may reduce disease recurrence at 12 mo or less - uncertain if improves disease recurrence at 12 months or less (EEC stage)	
(Tanmahasamut, *et al.*, 2012)	RCT	55 patients with endometriosis and moderate-to-severe dysmenorrhea (visual	After surgery, patients were randomized to a levonorgestrel-releasing intrauterine system (n =	Primary outcome: change of dysmenorrhea visual analog scale.	At 12 months follow-up: LNG-IUS group :		

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
		analog scale, greater than 50 mm) undergoing laparoscopic conservative surgery. two groups were comparable in age, BMI, parity, and baseline pain scores.	28) or expectant management (n = 27) group.	Secondary outcomes : pelvic pain VAS, dyspareunia VAS, Short Form-36 score, and adverse effects.	- a significantly lower median value of dysmenorrhea and noncyclic pelvic pain score, - greater reduction in dysmenorrhea VAS (-81.0 compared with -50.0 mm) - reduction in pelvic pain VAS (-48.5 compared with -22.0 mm). - Reduction in dyspareunia VAS was comparable between the groups. - 2 LNG-IUS (7.4%) and 9 expectant management (39.1%) had recurrent dysmenorrhea within 1 year postoperatively		

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	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. (Low quality evidence) Quality of evidence: ⊕⊕◯◯
Balance between desirable and undesirable outcomes	No proven harm of postoperative medical treatment May be beneficial for secondary prevention, and/or contraception
Balance between different outcomes	With no data on harm, and possible other benefits, a weak recommendation was formulated in favor of postoperative hormone treatment.
Patient values and preference	Unclear, no data
Resource use, equity, acceptability and feasibility	It seems that hormone treatment is acceptable and feasible in general, although the costs and availability may vary between countries.
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.**

Question II.5 Are surgical therapies more effective than medical therapies for women with endometriosis with pain symptoms?

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Vercellini, *et al.*, 2018)	Cohort	87 Women, 50 women medical treatment and 37 women surgery. Inclusion criteria: 18–50-year-old women not wanting pregnancy, who received an indication for surgical excision of intestinal endometriosis, The diagnosis of deep intestinal endometriosis was based on rectal endosonography to define the level of rectal involvement and to determine the depth of rectal wall infiltration; Subjects with persistent, cyclic or non-cyclic intestinal symptoms of more than 6 months duration, and an instrumental diagnosis of endometriosis infiltrating the muscular layer of the proximal rectal tract (≥8 cm from the anal verge), the rectosigmoid junction (13–15 cm from the anal verge) and the sigmoid (>15 cm from the anal verge) were deemed eligible for the study. Nodules of the distal rectum (within 8 cm from the anal verge) were not included. Exclusion criteria were: bowel stenosis associated with obstinate sub-occlusive symptoms (e.g. nausea and vomiting not limited to the days of menstruation, frequent episodes of colicky pain with abdominal distension (>1 per month), habitual emission of small-calibre stool); detection of ≥60% stenosis of the bowel lumen independently of sub-occlusive symptoms (Fig. 1); previous surgery for intestinal endometriosis; previous endoscopy-based diagnosis of chronic inflammatory bowel diseases (Crohn's disease; ulcerative colitis); evidence of complex adnexal cysts or an ovarian endometrioma of diameter >4 cm at vaginal ultrasonography; the typical	A total of 50 patients chose treatment with an OCP (n = 12) or a progestin (n = 38), whereas 37 women confirmed their previous indication to surgery. Patient satisfaction was graded according to a 5-category scale. Variations in bowel and pain symptoms were measured by means of a 0–10 numeric rating scale. Constipation was assessed with the Knowles–Eccersley–Scott Symptom Questionnaire (KESS), health-related quality of life with the Short Form-12 questionnaire (SF-12), psychological status with the Hospital Anxiety and Depression scale (HADS) and sexual functioning with the Female Sexual Function Index (FSFI)	Satisfaction	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. . Intestinal complaints were ameliorated by both treatments. Significant between-group differences in favour of medical treatment were observed at 12-month follow-up in diarrhoea, dysmenorrhoea, non-menstrual pelvic pain and SF-12 physical component scores. The total HADS score improved significantly in both groups, whereas the total FSFI score improved only in women who chose medical therapy.	Long term treatment with low- dose OCP or a progestin should be systematically included among the therapeutic options for women not seeking a conception with bowel endometriosis and without persistent and severe sub-occlusive symptoms. Surgery should be considered as a second line treatment. However final desicion should made together with the women.	Financed by Italian fiscal contribution.

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
		contraindications to oestrogen-progestins; and unwillingness to tolerate menstrual changes.					
(Vercellini*, et al.*, 2012b)	RCT	154 patient 51 patient repeat sugery group 103 patient progestin treatment group Age; 35.0+4.7 and 34.3+5.0 years Inclusion criteria: 18- 40 years old, women not wanting pregnancy, who had undergone larascopy or laparotomy for stage 3 or 4 endometriosis in the previous 24 months. Patients in whom rectovaginal lesions were not excised. Exclusion criteria were obstructive uropathy or symptomatic bowel stenosis; evidence of complex adnexal cysts or an ovarian endometrioma of diameter .4 cm at vaginal ultrasonography; therapies for endometriosis other than non-steroidal antiinflammatory drugs (NSAIDs) in the 3 months before study entry (6 months for GnRH analogues); the typical contraindications to progestins; the use of drugs that interfere with ovarian steroid metabolism; allergy to components of the study medication or to NSAIDs; abnormal findings at breast examination and mammary ultrasound scan; an abnormal cervical smear; a diagnosis of concomitant pelvic inflammatory disease, pelvic varices or genital malformations at previous surgery; known gastrointestinal, urologic and orthopedic diseases; psychiatric disturbances; history of drug or alcohol abuse; and unwillingness to tolerate menstrual changes.	12 months follow up, Participants who chose hormonal treatment were instructed to take 2.5 mg of oral norethisterone acetate once a day, starting on the first day of menstruation. At the 3-, 6- and 12-month evaluation the patients underwent clinical assessment, vaginal and rectal examination, and transvaginal ultrasonography, and were requested to indicate the frequency of intercourse (number per month), and to complete the pain questionnaire again	Pain scores	: In the surgery group, a marked and rapid short-term dyspareunia score reduction was observed, followed by partial recurrence of pain. The pain relief effect of the progestin was more gradual, but progressive throughout the study period. At a 12-month follow-up, the frequency of intercourse per month (mean+SD) was 4.6+1.8 in the surgery group and 5.3+ 1.5 in the norethisterone acetate group (P ¼ 0.02).	In conclusion, based on our observations we suggest that both surgical and progestin treatment are offered to women with deep dyspareunia and rectovaginal endometriotic lesions, i.e. in those with a mainly organic type of pain, whereas we strongly support the use of medical therapy as a first-line alternative for those without rectovaginal lesions, i.e. with a predominant inflammatory and functional component. Surgery remains the only possible option for women desiring a spontaneous conception. The combination of surgical and long-term adjuvant medical therapy deserves further research. In fact, such association may reveal the best available treatment, and the results of the present study appear to provide new arguments in favour of this strategy	

INCLUDED AS BACKGROUND INFORMATION
(van Barneveld*, et al.*, 2020)

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	Two low quality studies included: both not randomized; patients chose treatment arm; small sample sizes; no predetermined endpoints; not powered.

Balance between desirable and undesirable outcomes	Benefits with regards to pain relief / impact on disease progression versus risk (side-effects, surgical complications)
Balance between different outcomes	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 hospitalization, but it can be associated with short and long-term side effects and patients may need to use medical treatments for a long period. No evidence that either approach has an impact on disease progression. Advice is formulated as a GPP
Patient values and preference	Shared decision-making approach recommended
Resource use, equity, acceptability and feasibility	Consider costs of each approach and availability (different across countries)
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 between hormone treatments and surgical treatments for endometriosis-associated pain.**

QUESTION II.6 WHAT NON-MEDICAL MANAGEMENT STRATEGIES ARE EFFECTIVE FOR SYMPTOMS ASSOCIATED WITH ENDOMETRIOSIS (PAIN AND QUALITY OF LIFE)?

INCLUDED AS BACKGROUND INFORMATION
(Armour, *et al.*, 2019b, Barlow, *et al.*, 2005, Cox, *et al.*, 2003, Dunselman, *et al.*, 2014, Greco, 2003, Horne, *et al.*, 2017, Schwartz, *et al.*, 2019)

Summary of Findings Table

NOT APPLICABLE

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
ACUPUNCTURE							
(Xiang, *et al.*, 2002, Zhu, *et al.*, 2011)	Systematic literature review, RCT, only one RCT met the inclusion criteria	Endometriosis diagnosed on laparoscopy, 67 patients	Chinese drugs (30) vs auricular acupuncture (37). No placebo	VAS and dysmenorrhea	No differences between the two interventions, some decrease in dysmenorrhea	The review concluded that there was insufficient high quality evidence to recommend acupuncture for patients with endometriosis. They also established that a trail would need several hundred patients to reach a clinically credible estimate of efficacy.	
(Lund and Lundeberg, 2016)	Systematic literature review, Meta-analysis	3 papers included (Wayne, Rubi-Klein and Highfield (case studies 2 adolescent?)	Different acupuncture points/protocols	primary outcome VAS		No support for what kind of acupuncture, can be pain relieving, overall safe	
(Rubi-Klein, *et al.*, 2010) included in (Lund and Lundeberg, 2016)	RCT, cross over	n=101 47 sham acupuncture vs 54 verum (Chinese) acupuncture, endo confirmed on lap and P>5/10	5 weeks, 10 sessions, cross over after 2 menstrual cycles, acupuncture according to TCM (Traditional Chinese Medicine specifically described points) vs 'sham' which was acupuncture (non-specific points not related to endometriosis) by Austrian GPs with an	Pain (VAS) and disability SF36 and Pain Disability Index (PDI)	Significant decrease in pain VAS in verum group compared to non-specific, improvement in 7 out of 8 items on SF-36 (not physical role), unclear if statistically significant in item (social efficiency (p=0.065) other than psychological well being (p<0.05). Significant verum effect on PDI. No change in absentee. Decrease in use of analgesic in verum group.	Using specific acupuncture points provides significantly more pain relief and improvement in disability scores on the PDI and psychological well-being on SF-36.	No mention of randomisation, unable to blind, 18 drop outs (11 gained no benefit, 7 pregnant). Questions around the use of non-

			average of 5 years training		2 patients reported hypotonic side-effects but no relapse.		specific acupuncture points as 'sham'.
(Wayne, *et al.*, 2008) included in (Lund and Lundeberg, 2016)	RCT, placebo SHAM acupuncture/not penetrating	ADOLESCENT 13-22 years old. n=18 endo on lap, 4 drop outs, so 10 active, 8 sham	Japanese acupuncture (smaller needles and herbs) versus sham acupuncture (not penetrating the skin) 16 sessions, 2 per week over 8 weeks	VAS, Endo severity scale, lap, Pead QoL EHP-30 reviewed at 6 months as well	Considerable reduction in pain in the 1st week. Pain reduction was retained at 6 months but no statistical difference in groups	Japanese acupuncture is a safe and effective adjunct therapy for endometriosis-related pain	No data tables, no blinding, no adverse effects
(Xu, *et al.*, 2017)	Systematic literature review	10 studies; 1 Boston study (Wayne et al study) , 9 Chinese (not translated) 13-52 years old, not all endo specific, only 1 study used placebo and blinded assessors but it was a pilot	Chinese acupuncture versus Western medicine (danazol, mifepristone, or goserelin acetate) , sham or Chinese herbs (varied control groups)	varied, pain VAS, CA-125 enzyme, Combined Traditional Chinese and Western medicine in the treatment of endometriosis: (1991) (cured, markedly effective, effective, failed)		Only 1 sham acupuncture, no blinding, Chinese acupuncture better than Western medicine in pain relief and reduction in CA-127 enzyme, small sample sizes (10-35/8-35)	
PHYSICAL THERAPIES							
(Denneny, *et al.*, 2019)	Systematic Review and Meta-analysis	Chronic Noncancer Pain patients (inclusion; patients older than 18, with pain of 3 months' duration or more) 19 trials (1047 participants)	Trigger Point Manual Therapy	pain, function, and patient-reported improvement	No effect was found for short-term pain relief (mean standardized difference (MSD) -0.53; 95% CI, -1.08 to 0.02). One small study : longer-term benefit for pain (MSD -2.00; 95% CI, -3.40 to -0.60) (low confidence in the effect) Function (MSD -0.77; 95% CI, -1.27 to -0.26) (significant gains, 4 studies) Patient global response (odds ratio 3.79; 95% CI,1.86-7.71) (significant gains, 4 studies) Health-related quality of life : no effect	Evidence for TPMT for chronic noncancer pain is weak and it cannot currently be recommended.	Literature search up to May 2017
(Loving, *et al.*, 2012)	Systematic review	Chronic pelvic pain (CPP)	Physiotherapy (in combination with psychotherapeutic	pain improvement	Some evidence to support an effect of multidisciplinary intervention and Mensendieck	'stand-alone' value of physiotherapy could not be determined.	Meta-analysis was not feasible

		11 articles, representing 10 studies, met the inclusion criteria. (6 RCTs, 1 cohort study and 3 case series.)	modalities and medical management)		somatocognitive therapy on female chronic pelvic pain		
(Armour, *et al.*, 2019a)	Cochrane review	Dysmenorrhoea. 10 studies included in the quantitative analysis	Exercise versus no treatment, attention control, NSZAIDs or OCP	Menstrual pain intensity Adverse events *Overall menstrual symptoms* *Use of rescue analgesic medication* *Absence from work or school* *Quality of life*	Exercise may have a large effect on reducing menstrual pain intensity compared to no exercise (SMD -1.86, 95% CI -2.06 to -1.66; 9 RCTs, n= 632; I2= 91%; low-quality evidence). There was evidence that high-intensity exercise provided a greater reduction in menstrual pain intensity than low-intensity exercise (P = 0.0001). One study reported on adverse events; no participants in either group reported any adverse events	exercise, undertaken regularly throughout the month, may provide a large and clinically significant reduction in menstrual pain intensity when compared to no treatment. No evidence that the type of exercise (high-intensity versus low-intensity) provided any difference in benefit. Insufficient evidence to determine whether exercise reduced menstrual pain intensity compared to NSAIDs	
(Bonocher, *et al.*, 2014)	Systematic review	Lit 1985-2012 included 6 observational studies	physical exercise	Risk for developing endometriosis improvement of the symptoms associated with endometriosis.	one study showed decreased risk of endometriosis with exercises, one recommended to AVOID strength, one showed protective in menarche, one showed 3 x weekly protective	The data available are inconclusive regarding the benefits of physical exercise as a risk factor for the disease and no data exist about the potential impact of exercise on the course of the endometriosis. Randomized studies are necessary.	Included studies; Cramer 1986; Han 1994; Signorello 1997; Dhillon and Holt 2003; Vitonis 2010; Koppan 2010
(Koppan, *et al.*, 2010) Included in (Bonocher, *et al.*, 2014)	Cohort study	150 patients with endometriosis, diagnosed on laparoscopy	looking at lots of interventions, meds, sports participation and symptoms	na	80-85% do improve, pain killers less effective when doing sport	Taking painkillers might be less effective among endometriosis patients performing regular daily sport activities	
(Goncalves, *et al.*, 2017)	RCT	40 patients with endometriosis,	28 patients; yoga 8 weeks, twice weekly (see above qual study)	Pain, QoL EHP-30	The degree of daily pain was significantly lower among the women who practiced yoga	Yoga practice was associated with a reduction in levels of	Randomisation yes, blinding,

		diagnosed on laparoscopy	12 control (meds and physio)		compared with the non-yoga group (p= 0.0007). There was an improvement of QoL in both groups between baseline and the end of the study. In relation to EHP-30 domains, pain (p= 0.0046), impotence (p =0.0006), well-being (p=0.0009), and image (p=0.0087) from the central questionnaire, and work (p=0.0027) and treatment (p=0.0245) from the modular questionnaire were significantly different between the study groups over time. There was no significant difference between the two groups regarding the diary of menstrual patterns (p =0.96).	chronic pelvic pain and an improvement in QoL in women with endometriosis.	small number, short term useful
(Goncalves, *et al.*, 2016)	Qualitative (semi-structured interview, self-reported benefits)	15 women with pain-associated endometriosis	YOGA twice weekly 8 weeks	- women's expectations regarding the practice of yoga, - control and pain management through - the integration of body and mind, - secondary benefits, acquisition of self-knowledge and autonomy, role of yoga group as psychosocial support.	- yoga was beneficial to control pelvic pain - greater self-knowledge, autonomy, and self-care and have reduced the use of pain and psychiatric medications.	Bonding with group, breathing, reduction in tension, self-care and knowledge, awareness	
(Awad, *et al.*, 2017)	Trial before and after	20 pelvic pain endometriosis on laparoscopy, one group design, no control	The exercise program included posture correction exercises), diaphragmatic and lateral costal breathing exercises, general relaxation and teaching muscle sense, Diversion drill training,	Pain VAS score from 4 to 1, kyphosis angle	statistically significant difference in pain level among the three measuring periods (pre and post 12 sessions of treatment, and post 24 sessions) (p<0.025). statistically significant reduction in the pain level in		Any interventions providing 24 sessions of support should show a trend of Pain reduction

			positional education on cross-sitting and squatting positions),stretching exercises, treadmill walking sessions 3 times/week + home exercises 24 sessions in total		the post 24 sessions of treatment compared with the pre treatment and post 12 sessions of treatment ($p<0.025$). statistically significant reduction in the pain level in the post 12 sessions of treatment compared with the pre-treatment ($p<0.025$).		
(Carpenter, *et al.*, 1995)	RCT	39 patients with endometriosis, diagnosed on laparoscopy, no previous exercise	danazol versus danazol with exercises exercises: 40 min, 4 x weekly, individualised exercises	testosterone levels during treatment side-effects of danazol (during a 4-week period) endometriosis recurrence	Testosterone levels: signif lower in danazol/exercise group. Number of side effects: 1.09-2.17 times greater for the danazol-only group. Time to recurrence : no difference All patients had improvement of symptoms	Exercise had positive effect on decreasing the androgenic effect and side-effect as well as delaying endometriosis recurrence	
(Darai, *et al.*, 2015)	Prospective pilot osteopathic	n=20 pts, 5 drop outs, deep infiltrating endometriosis	osteopathic manipulative therapy	sf-36	After a mean period of 24 days (15–53), a significant improvement in Physical Component Summary (PCS) ($p = 0.03$) and Mental Component Summary (MCS) ($p = 0.0009$) compared to pre-OMT values was observed giving a success rate of 80% and 60% in intention-to-treat, resp.	OMT can improve QOL of patients with DE and colorectal involvement.	pilot only, indicate that a study could be useful
(Valiani, *et al.*, 2010)	Cohort, observational (semi-empirical clinical trial.)	n=23 endometriosis patients confirmed by laparoscopy	20 minute massage	VAS, McGill before, immediately after and 6 weeks after	a statistically significant difference between the intensity of pain before the intervention started, immediately after, and also six weeks after it ($p < 0.001$).	massage therapy can be a fitting method to reduce the menstrual pain caused by endometriosis.	Small, low quality study
ELECTROTHERAPY							
(Mira, *et al.*, 2015)	non-blind RCT	22 endometriosis patients (DE with persistent, chronic pelvic pain and deep	Randomised to self-applied TENS (11) or acupuncture-like TENS	Visual Analogue Scale, Deep Dyspareunia Scale and Endometriosis Quality	No drop outs, For both interventions;	Both interventions demonstrated effectiveness as a complementary	

		dyspareunia despite hormone therapy	(11), twice daily 20 min, 4 wks	of Life Questionnaire (ENDO HEALTH).	Decrease in VAS, some improvements in QoL after 8 weeks, no change in dysmenorrhea	treatment of pelvic pain and deep dyspareunia, improving QoL in women with DE regardless of the device used for treatment.	
(Nnoaham and Kumbang, 2008)	Cochrane review	chronic pain	Transcutaneous Electrical Nerve Stimulation (TENS)	Pain symptoms	na	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.	
(Bi and Xie, 2018)	Retrospective,	n=154 patients with biologically confirmed endometriosis and pain 83 in treatment group and 71 waiting list controls	10 weeks of neuromuscular electrical stimulation (NMES) (motor nerves, acupuncture points medical malleoili and abdomen, 30 min 3 x weekly No mention of control interventions	Pain on numeric rating scale (NRS), Endometriosis Symptom Severity Scale (ESSS), SF-36	After 5-week treatment, no significant differences in all outcome measurements were found between the 2 groups. After 10-week treatment, NMES therapy exerted better outcomes in NRS (P=.02), ESSS (P=.04), and SF-36 [Physical Component Summary (PCS), P<.01; Mental Component Summary (MCS), P<.01], compared with the patients at the waiting list. No significant differences of all adverse events were found between the 2 groups, although mild and acceptable adverse events occurred in the treatment group.	No effect after 5 weeks, then a significant effect in all measures after 10 weeks though results presented so unable to conclude. No or minimal adverse events reported. 'tolerable'	
(Thabet and Alshehri, 2018)	RCT	n=40 mild or moderate endometriosis	20 women : pulsed high-intensity laser therapy (HILT) 3 times per week for 8 weeks, as well as the usual regimen of hormonal treatment given to endometriosis patients,	EHP-5, Present Pain Intensity (5 point scale), Pain Relief Scale and laparoscopic endometriosis ASRM Medicine score	Improvements in PRS, EHP-5 and laparoscopic endometriosis reduced - all significantly compared to sham laser treatment	Pulsed high-intensity laser therapy is an effective method of pain alleviation, reducing adhesions, and improving the quality of life in women with endometriosis.	No blinding of therapist, small sample, difficult to interpret results

			20 women sham laser treatment + usual regimen of hormonal treatment.				
PSYCHOLOGY							
(Buggio, *et al.*, 2017)	narrative review	endometriosis	psychological interventions, including psychotherapy			importance of integrating psychological interventions, including psychotherapy, in endometriosis treatment. The authors suggest that women may benefit from supportive–expressive psychotherapeutic interventions (either individual or group interventions) aimed at facilitating the expression of deepest thoughts and feelings about endometriosis, as well as at empowering their female identity.	
(Van Niekerk, *et al.*, 2019)	systematic review, with narrative data synthesis	11 full-text studies that met inclusion criteria	psychological interventions	Relief of endometriosis-related symptoms		the overall quality of studies was found to be 'weak', with a 'high' risk of bias. The findings regarding the effectiveness of psychological interventions for endometriosis-related symptoms remain inconclusive.	
(Evans, *et al.*, 2019)	review	women with endometriosis 12 publications relating to 9 separate studies	interventions that used psychological and mind-body (PMB) interventions: yoga, mindfulness, relaxation training, cognitive behavioural therapy combined with physical therapy, Chinese medicine	endometriosis pain, psychological distress, sleep and fatigue.	these pilot studies suggest that PMB interventions show promise in alleviating pain, anxiety, depression, stress and fatigue in women with endometriosis	no studies have yet used gold-standard methodology and, thus, definitive con-clusions cannot be offered about PMB efficacy	PsychINFO, MEDLINE, CINAHL, EMBASE, Cochrane Library, Scopus, and PubMed.

			combined with psychotherapy, and biofeedback.				Studies were identified and coded using standard criteria, and risk of bias was assessed
(Beissner, *et al.*, 2017)	RCT	67 patients with endometriosis, diagnosed on laparoscopy, severe pain, 35 intervention - 32 waiting list controls	CBT, hypnosis, problem solving and acupuncture (CHINESE medicine) 4 sessions of 60 min	Pain, Disease-Related Quality of Life, and psychological measures (Depression, Anxiety, Stress) and fMRI	significantly larger improvements for all of the above-mentioned outcomes in the treatment group as compared with the control subjects (all p , .05). Effect sizes were medium to large.	putative neurobiological mechanism underlying the potent combination of psychotherapy and somatic stimulation in treating symptoms of endometriosis.	
(Meissner, *et al.*, 2016)	RCT	women with histologically confirmed endometriosis and chronic pelvic pain 31 intervention, 29 waiting list controls	3 months mindfulness based psychotherapy, prob solving, CBT+ Chinese acupuncture/cupping, heat and increased self-care	brain connectivity was primary outcome, pain, dyschezia, HAD SF-12 FU until 24 months	In comparison with wait-list controls, treated patients showed improvements after 3 months in maximal global pain (mean group difference22.1, 95% CI[CI] 23.4 to 20.8; P=.002), average global pain (22.5,95% CI 23.5 to 21.4; P=.001), pelvic pain (21.4, 95% CI 22.7 to 20.1; P=.036), dyschezia (23.5, 95% CI 25.8 to 21.3; P5.003), physical quality of life (3.8, 95% CI 0.5–7.1,P=.026), and mental quality of life (5.9, 95% CI 0.6–11.3; P=.031); dyspareunia improved nonsignificantly (21.8,95% CI 24.4 to 0.7; P=.150). Improvements in the intervention group remained stable at 6 and 24 months	dyschezia, global pain, QoL improved significantly dyspareunia non-significant stable improvements at 6 and 24 months	Not blinded, treatment effect to wait list
(Lorençatto, *et al.*, 2007)	Two-arm retrospective stduy	128 Women with surgically confirmed endometriosis and persistent pelvic pain	multi-professional group intervention (10 sessions)	Pain (VAS) Depression (BDI-II)	A significant moderate effect reported as reduction in pain and depression for the intervention group. Pain and depression positively correlated for both groups		Non-English study, data as reported by Van Niekerk 2019
(Hansen, *et al.*, 2017)	Follow up of an intervention study	10 women with endometriosis and CPP	10 sessions of mindfulness-based	12 month and 6 year follow up	results showed no significant differences in mean scores on all scales of the EHP-30	mindfulness-based psychological treatment of	

			psychological intervention	Quality of life (endometriosis specific questionnaire EHP-30 and the generic form SF-36)	and almost all scales of the SF-36 scale scores. The results indicate lasting improvement on almost all scales of the EHP-30 and the SF-36.	chronic pain seems very relevant to improve QoL	
(Meissner, *et al.*, 2010)	retrospective	47 patients with severe endometriosis	Traditional Chinese Medicine and Hypnotherapy	Pain scores Use of pain medication Pregnancy Median follow-up time was 5 years.	The median intensity of endometriosis-associated pain had decreased from 8 to 3 points on a 0–10 point VAS ($p < 0.001$). 18 patients (38%) were free of pain, and the number of patients using pain medication had decreased from 38 to 19 (from 81% to 40%). 17 out of the 31 women trying for a pregnancy (55%) showed a total of 21 births at follow-up. Exploratory analyses revealed a possible dose-response relationship.	Treatment of endometriosis with a holistic approach of Chinese medicine and hypnotherapy may result in a substantial reduction of pain as well as increased birth rates in patients with therapy-refractory endometriosis.	No control group
(Farshi, *et al.*, 2020)	RCT	76 endometriosis patients	self-care counselling (7 self-care group counselling sessions were held on a weekly basis) versus control group (routine care)	effect on anxiety and QoL	the mean scores of state anxiety (mean difference: − 0.12, 95% CI − 9.6 to − 14.4, $p < 0.001$) and trait anxiety (MD − 10.9: 95% CI: − 9.1 to − 12.7, $p = 0.001$) were significantly lower in the counselling group The mean score of depression was lower in the counselling group than in the control group; however, it was not significant (p = 0/565). The mean score of quality of life for physical health (MD =17.2, 95% CI 13.8 to 20.5, $p < 0.001$) and for mental health (MD 12.0, 95% CI: 9.0 to 14.9, $p < 0.001$) were significantly higher in the	Self-care counselling affects the anxiety and quality of life of women with endometriosis. Therefore, in addition to other therapies, this method is proposed to improve quality of life and mental health of patients with endometriosis.	

					counselling group than in the control group.		
(Friggi Sebe Petrelluzzi, *et al.*, 2012)	obs	26 patients with endometriosis, diagnosed on laparoscopy with pain symptoms	10 wk 2.5 hrs, physio(TENS, posture, breathing, self-m)1 hr, psych CBT,	VAS, SF 36, Cortisol in saliva	?	decrease in VAS and cortisol, no change in SF36, increased physical function	NO control, no follow-up
NUTRITION							
(Hansen and Knudsen, 2013)	Meta-analysis	1433 papers reviewed - 23 articles used, used cocraine analysis techniques	inclusion exclusion was sparse, study period variable	variable outcome measures, different pain scoring tools, recall of nutritional intake which may cause bias. Some did not stratisfy for weight and oral contraceptives and analgesia		litrature sugests that increased 3-Fas, fish oils and PUFAs has positive effect on endo and dysmen indicating that their may be modifyable risk factors - further research is needed	
(Huijs and Nap, 2020).	systematic review	12 included studies (4 RCTs, 4 non-randomized CTs, 1 retrospective study, 1 case series and 2 case reports) Incl: women with surgically or MRI/US confirmed endometriosis - English studies in a peer-reviewed journal.	nutrient or diet Fatty acids, antioxidants, gluten, and soy	Effect on endometriosis-related symptoms	Fatty acids (4 studies) 3 studies (n= 112, aged 24–61) of palmitoylethanolamine and transpolydatin: lower VAS compared to controls 1 study, alpha-lipoic acid, palmitoylethanolamide and myrrh: VAS for CPP and dysmenorrhoea decreased, no impact on cyst volume. Antioxidants: Case series (n=8) : no conclusion Gluten: 1 case report Soy: 2 women	In 9 studies, nutrients were added to patients' diets, and in 7 of these a positive effect was found. In 3 studies, nutrients (soy, gluten and FODMAP) were avoided, with positive effects on symptoms	PubMed and Cochrane up to March 2019
(Nodler, *et al.*, 2020).	RCT	69 Women (aged 12–25y) with surgically confirmed endometriosis and pelvic pain	Randomly assigned to - vitamin D3 (n=27) - fish oil (Omega-3 fatty acids supplement) (n=20) placebo. (n=22)	Pain (VAS) Quality of life Pain catastrophizing Pain medication usage	improvement in VAS pain from baseline to 6 mo (mean (95% CI)): - vit D : 7.0 (6.2, 7.8) to 5.5 (4.2, 6.8), P = 0.02 - fish oil : 5.9 (4.8, 7.0) to 5.2 (3.7, 6.8), P = 0.39 - placebo: 6.0 (5.1, 6.9) to 4.4 (3.0, 5.8),P = 0.07. No diff between interventions and placebo	Study reports a significant improvement in pain scores after vitamin D supplementation, but also a similar effect in the placebo group A more modest improvement in patients receiving fish oil	

(Savaris and do Amaral, 2011)	observational study	n=45 - 2 groups 25 active and 20 control -	study duration not recorded	Calorie and nutrition intake and blood tests weight and skin folds		nil conclusions, observed greater fiber intake in endometriosis group. and highter in take of polyunsaturated fatty acid in the control group	
(Mier-Cabrera, *et al.*, 2009).	RCT cross over	n-163 control group were post tubal ligation without endometriosis	hight oxidant diet 4 months,	/	women with endo had a lower anti oxidant diet than women without endo - when given diet rich in anti-oxidants their levels increase in their blood and plasma		nil details of pain
(Schink, *et al.*, 2019).	retrospective case-control study	156 women with endometriosis 52 age-matched controls	nutrient intake information on food intolerances, allergies, and gastrointestinal symptoms	/	nutrient intake: in endometriosis, lower intake of animal proteins, vitamin C, vitamin B12 and magnesium in endometriosis, higher prevalence of food intolerances (25.6% vs 7,7%) and allergies (57% vs 31%) and gastrointestinal symptoms (77% vs 29%)	a dietary intervention by a professional nutritionist may help to reduce disease burden in women with endometriosis	
(Vennberg Karlsson, *et al.*, 2020)	qualitative study	12 women with endometriosis (28 to 44 yo) (Sweden)	Motivation to make and maintain dietary changes		participants experienced decreased symptoms of endometriosis (pain and fatigue) and gained a greater understanding of their bodies after making individual dietary changes	Healthcare professionals should take their patients' knowledge and experience into consideration, and allow patients to participate in their own care.	
TRADITIONAL CHINESE MEDICINE							
(Flower, *et al.*, 2011).	Feasibility Study	2 (private) centre study Women with endometriosis and pain >4cm on VAS	Herbs (n=15) versus Placebo (n=18) with Waiting list control (n=13) over 16 weeks. Herbs = individualized Chinese medicine decoctions Placebo = therapeutically inert placebo decoction.	10cm VAS, EHP-30, MYMOP and blood tests Side effects	There were no serious adverse reactions or any abnormal liver or renal function test results in women taking the active CHM. For VAS scores, both groups showed clinically relevant reductions in pain on intercourse. A relevant reduction in period pain was only apparent in the active group.	Nil conclusions could be drawn - suggested a larger study	Pilot study, underpowered, High nr of drop outs

(Zhao, *et al.*, 2013)	RCT	Endometriosis diagnosed on laparoscopy	136 Chinese medicine (CM) vs 141 Western medicine (hormones) (WM) 3-6 months therapy	WHO's QOL-BREF (before vs after scores)	CM group: bigger improvements in general QoL general, sexual activity, mobility, activities of daily living, pain Western Medicine group; No significant changes in sex, activities of daily living and mobility After treatment, the scores for physical health in the CM group were significantly higher than those of the WM group ($P < 0.05$) and the scores of 4 items (mobility, activities of daily living, sexual activity, QOL score) in the CM group were significantly higher than those in the WM group ($P < 0.05$). (but pretreatment differences between groups)	CM and WM treatment could improve the QOL of patients with endometriosis after conservative surgery. CM treatment is more effective than WM.	Unfamiliar outcome measure, no blinding, no placebo

INCLUDED AS BACKGROUND INFORMATION
(British Pain Society, 2019) (Dumoulin, *et al.*, 2018, National Institute for Health and Care Excellence, 2007, In development [GID-NG10123])

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	There is a lack of research specifically addressing the impact of non-medical strategies in the treatment of endometriosis-related symptoms Some (low-quality) evidence or anecdotal evidence of a benefit for symptoms and pain.
Balance between desirable and undesirable outcomes	Benefits with regards to pain relief should be balanced against the risks

Balance between different outcomes	There is little evidence on the benefits. There is no evidence of harm, but not well studied/reported
Patient values and preference	It seems evident that women are searching for alternative ways of managing and coping without or alongside surgical and pharmacological interventions. The GPP 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
Resource use, equity, acceptability and feasibility	The recommendation is similar to those of other societies/organisations
RECOMMENDATION	**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.**

QUESTION III.1 ARE HORMONE/MEDICAL THERAPIES EFFECTIVE FOR TREATMENT OF ENDOMETRIOSIS-ASSOCIATED INFERTILITY?

INCLUDED AS BACKGROUND INFORMATION
(Tomassetti and D'Hooghe, 2018)

Ovarian suppression

Summary of Findings Table

III.1a Ovarian suppression agents compared to placebo or no treatment for increasing natural fertility in women with endometriosis

Patient or population: endometriosis-associated infertility
Intervention: ovulation suppression agents
Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no treatment	Risk with ovulation suppression agents				
Clinical pregnancy rate	203 per 1,000	198 per 1,000 (148 to 259)	OR 0.97 (0.68 to 1.37)	833 (12 RCTs)	⊕⊕◯◯ LOW [a,b]	(Hughes, *et al.*, 2007)
Clinical pregnancy rate (infertile couples/those desiring pregnancy only)	270 per 1,000	274 per 1,000 (204 to 357)	OR 1.02 (0.69 to 1.50)	557 (11 RCTs)	⊕⊕◯◯ LOW [a,b]	(Hughes, *et al.*, 2007)
Outcomes	Risk with placebo or no treatment	Risk with ovulation suppression agents (excluding Danazol)	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Clinical pregnancy rate	156 per 1,000	159 per 1,000 (113 to 220)	OR 1.02 (0.69 to 1.52)	781 (9 RCTs)	⊕⊕◯◯ LOW [a,b]	(Hughes, *et al.*, 2007)
Clinical pregnancy rate (infertile couples/those desiring pregnancy only)	231 per 1,000	249 per 1,000 (174 to 343)	OR 1.10 (0.70 to 1.73)	436 (8 RCTs)	⊕⊕◯◯ LOW [a,b]	(Hughes, *et al.*, 2007)
Outcomes	Risk with OCP	Risk with GnRH agonist	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Live birth rate	289 per 1,000	219 per 1,000 (96 to 429)	OR 0.69 (0.26 to 1.85)	86 (1 RCT)	⊕⊕◯◯ LOW [c]	(Hughes, *et al.*, 2007)

Explanations
a. Relatively small and older studies with possible methodological issues (as identified in the Cochrane review).

b. Inconsistency in the direction of effect of the included studies
c. Single small trial

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Hughes, *et al.*, 2007)	Cochrane review	N=12 RCTs Women with visually diagnosed endometriosis, either by laparoscopy or laparotomy, who had failed to conceive after 12 or more months of unprotected intercourse.	An ovulation suppression agents, including danazol, progestins and OCP versus placebo or no treatment. Trials where medical treatment was administered after surgical treatment for endometriosis were included.	pregnancy outcomes live births	See Summary of findings table No studies reported on live birth	no evidence of benefit of ovulation suppression agents on pregnancy outcomes, although data on live birth are not available.	

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	Suppression of ovarian function (by means of danazol, GnRH agonists, progestins, OCP) to improve fertility in women with endometriosis is not effective (Cochrane review) Risks/side-effects are as discussed in the section of medical treatment for pain Quality of evidence: ⊕⊕◯◯ (see SOF table)
Balance between desirable and undesirable outcomes	Effectiveness towards increasing pregnancy versus risks/side-effects of the medical treatment.
Balance between different outcomes	Based on the inefficacy of treatment, the intervention is not recommended.
Patient values and preference	Similar as included in the section of medical treatment for pain, however, based on the inefficacy of treatment, these outcomes are not discussed or considered
Resource use, equity, acceptability and feasibility	Similar as included in the section of medical treatment for pain, however, based on the inefficacy of treatment, these outcomes are not discussed or considered
RECOMMENDATION	**In infertile women with endometriosis, clinicians should not prescribe ovarian suppression treatment to improve fertility.**

Hormone or medical therapies as an adjunct to surgical therapy

Summary of Findings Table

III.1b Surgery + pre-surgical/post-surgical hormone suppression compared to surgery only for increasing natural fertility in women with endometriosis

Patient or population: increasing natural fertility in women with endometriosis
Intervention: surgery + pre-surgical/post-surgical hormonal suppression
Comparison: surgery only

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with surgery only	Risk with surgery + pre-surgical hormonal suppression				
Pregnancy rate	547 per 1,000	**646 per 1,000** (531 to 794)	**RR 1.18** (0.97 to 1.45)	262 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	**(Chen, *et al.*, 2020)**
Outcomes	**Risk with surgery only**	**Risk with surgery + post-surgical hormonal suppression**	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Pregnancy rate	344 per 1,000	**409 per 1,000** (351 to 475)	**RR 1.19** (1.02 to 1.38)	955 (11 RCTs)	⊕⊕⊕◯ MODERATE [c]	**(Chen, *et al.*, 2020)**

Explanations
a. Downgraded once for serious risk of bias – no blinding and trial lacked details on allocation concealment.
b. Downgraded twice for very serious imprecision – evidence based on a single trial, wide confidence interval, small number of events.
c. Downgraded once for risk of bias – there are inadequate details on blinding and attrition.

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Chen, *et al.*, 2020)	Cochrane review	25 trials in 3378 women with endometriosis Analysis effect of pre-surgical hormonal suppression on PR : 1 trial included in the analysis (Alkatout 2013) Analysis of post-surgical hormonal suppression on PR : 11 trials included in the analysis Analysis effect of pre-surgical vs post-surgical	medical therapies for hormonal suppression before, after, or both before and after therapeutic surgery	natural fertility	See Summary of findings table No studies reported on live birth	Results were inconclusive for hormonal suppression of endometriosis prior to surgery regarding pregnancy rate, with very low-quality evidence. The meta-analysis showed that postsurgical medical therapy group probably improves pregnancy rate, compared to no medical therapy, with moderate-quality evidence.	There is significant overlap between the studies included in Hughes 2007 and Chen 2020 , although they report on ovarian suppression and post-op ovarian suppression resp.

		hormonal suppression on PR : 1 trial included in the analysis (Alkatout 2013)					

INCLUDED AS BACKGROUND INFORMATION
(Furness*, et al.*, 2004)

EVIDENCE TO RECOMMENDATIONS – PRESURGICAL TREATMENT

The evidence (and its quality)	The review by Chen found no benefit of presurgical treatment with regards to pregnancy rates. Presurgical treatment is also not recommended for pain relief.
Balance between desirable and undesirable outcomes	Benefit (pregnancy) versus side effects
Balance between different outcomes	Considering there is no benefit with regards to pregnancy, nor pain relief, a recommendation was not further discussed, and the reader is referred to the recommendation formulated for pain management: "It is not recommended to prescribe preoperative hormone treatment to improve the immediate outcome of surgery for pain in women with endometriosis."
Patient values and preference	See above
Resource use, equity, acceptability and feasibility	No recommendation of a treatment without shown benefit
RECOMMENDATION	No recommendation

EVIDENCE TO RECOMMENDATIONS – POSTSURGICAL TREATMENT

The evidence (and its quality)	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. The review of Chen 2020 included pregnancy rate as outcome, and included both pregnancy rate from spontaneous conception and after MAR. As such, it was considered as indirect evidence for the outcome of live birth/pregnancy after natural conception, and downgraded. The fragile reported RR of 1.19 (1.02 to 1.38) was interpreted as evidence of no harm of ovarian suppression after surgery, rather than benefit. There is no evidence on the appropriate duration of treatment and the time to pregnancy. Delayed start of attempted conception due to hormonal suppression should be considered in decision-making. The GDG considers that the time to pregnancy/live birth would be the most important outcome for recommending postsurgical medical treatment, but found no evidence for that outcome. Quality of evidence : ⊕⊕◯◯

Balance between desirable and undesirable outcomes	The pregnancy rates after an additional treatment should be weight against side effects and possible longer time to pregnancy. The treatment may also have a benefit for pain relief.
Balance between different outcomes	Considering there is no evidence on the impact of treatment on the time to pregnancy, and the uncertain benefit it was decided not to recommend postoperative hormone suppression. When the impact of treatment on the time to pregnancy is not a factor, treatment may be considered for treatment of pain symptoms. (2 recommendations were formulated)
Patient values and preference	Women with subfertility due to endometriosis may not accept treatment that may reduce or delay their chance of conceiving after a surgical treatment
Resource use, equity, acceptability and feasibility	It seems widely accepted that medical treatment for endometriosis (ovarian suppression) does not increase the risk of future pregnancy. In addition, offering postsurgical treatment will have consequences for cost.
RECOMMENDATION	**Women seeking pregnancy should not be prescribed postoperative hormone suppression with the sole purpose to enhance future pregnancy rates.**
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.**

Other medical treatment

Summary of Findings Table

III.1c Medical therapy compared to placebo or no medical therapy for increasing natural fertility in women with endometriosis

Patient or population: increasing natural fertility in women with endometriosis
Intervention: medical therapy
Comparison: placebo or no medical therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no medical therapy	Risk with Pentoxifylline				
Clinical pregnancy	203 per 1,000	**380 per 1,000** (185 to 426)	**RR 1.38** (0.91 to 2.1)	285 (3 RCTs)	⨁◯◯◯ VERY LOW [a,b]	(Grammatis 2021)
Outcomes	**Risk with placebo or no medical therapy**	**Risk with Letrozole**	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Pregnancy	281 per 1,000	**233 per 1,000** (111 to 426)	**OR 0.78** (0.32 to 1.90)	104 (1 RCT)	⨁◯◯◯ VERY LOW [c]	(Alborzi 2011)
Outcomes	**Risk with placebo or no medical therapy**	**Risk with Triptorelin**	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Pregnancy	281 per 1,000	**275 per 1,000** (132 to 484)	**OR 0.97** (0.39 to 2.40)	97 (1 RCT)	⨁◯◯◯ VERY LOW [c]	(Alborzi 2011)

Explanations
a. Two trials did not provide an adequate explanation of allocation concealment, and one study was deemed as at high risk of selection bias. Blinding was adequately described in only one trial; downgraded once for risk of bias
b. Small number of events and wide confidence intervals. Intention-to-treat analysis not performed in any of the included studies; downgraded twice for imprecision.
c. Single trial, small number of patients

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
{Lu, 2012 #551;Grammatis, 2021 #819}	Cochrane review	285 patients with endometriosis (3 studies)	Pentoxifylline	Clinical pregnancy	See summary of findings table	Our findings suggest there is uncertainty about the effect of pentoxifylline treatment on overall pain, and there were no data on live birth rate. We are uncertain ofthe effect of pentoxifylline on clinical pregnancy rate, miscarriage rate, or	*Lu 2012 was replaced by the more recent version of the review by Grammatis 2021*

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
						recurrence rate of endometriosis given the very low quality of the evidence. Subgroup analysis by duration of treatment and severity of endometriosis further highlighted the uncertainty ofthe effect of pentoxifylline on CPR.	
(Alborzi, *et al.*, 2011)	RCT	144 Infertile patients with laparoscopical and histological diagnosis of endometriosis who were infertile at least for 12 months and some of whom had symptoms such as dysmenorrhea, dyspareunia and pelvic pain Exclusion criteria: severe male factor infertility requiring ICSI or preoperative medication	After surgery : Aromatase inhibitor, letrozole, one tablet 2.5 mg/day for 2 months (n=47) GnRH analogue, triptorelin, Amp 3.75 mg (IM) every 4 weeks, for 2 months (n=40) No medication (n=57)	Pregnancy rate FU: at 3-month intervals for 1 year after restoration of menstruation cycles.	See summary of findings table Pregnancy rate : Letrozole: 11/47 (23.4%) Triptorelin: 11/40 (27.5%) No treatment:16/57 (28.1%) P=0.85 Interval from surgery to pregnancy (months) Letrozole: 5.5 ± 2.6 Triptorelin: 5.02 ± 4.02 No treatment: 5.9 ± 3.6 P=0.6	Pregnancy rate and Interval from surgery to pregnancy are comparable among the 3 groups.	

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	Studies show no benefit of pentoxifylline, post-operative aromatase inhibitor (letrozole), or post-operative GnRH agonist(triptorelin) to improve pregnancy rates.
Balance between desirable and undesirable outcomes	Efficacy (pregnancy rates) versus side-effects of treatment
Balance between different outcomes	Not assessed as intervention not effective
Patient values and preference	Similar as included in the section of medical treatment for pain, however, based on the inefficacy of treatment, these outcomes are not discussed or considered
Resource use, equity, acceptability and feasibility	Similar as included in the section of medical treatment for pain, however, based on the inefficacy of treatment, these outcomes are not discussed or considered
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.**

QUESTION III.2 IN WOMEN WITH ENDOMETRIOSIS, IS SURGERY EFFECTIVE TO INCREASE THE CHANCE OF NATURAL PREGNANCY?

Summary of Findings Table

III.2 Surgery compared to no surgery for increasing natural fertility in women with endometriosis

Patient or population: increasing natural fertility in women with endometriosis
Intervention: surgery
Comparison: no surgery

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no surgery	Risk with surgery				
Pregnancy (viable intrauterine pregnancy) assessed with US	186 per 1,000	**302 per 1,000** (223 to 396)	**OR 1.89** (1.25 to 2.86)	528 (3 RCTs)	⊕⊕⊕◯ MODERATE [a]	Based on Bafort 2020
Clinical pregnancy rate	349 per 1,000	**503 per 1,000** (433 to 586)	**RR 1.44** (1.24 to 1.68)	707 (6 RCTs)	⊕◯◯◯ VERY LOW [b,c,d]	Based on Yin 2014 (some overlapping data to Bafort 2020)

Explanations
a. Downgraded once for high risk of attrition bias.
b. Randomised and quasi-randomized studies combined
c. Inconsistency between the studies detected
d. Small studies with large confidence intervals

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Bafort, *et al.*, 2020a)	Cochrane review	Pain or infertility associated with endometriosis (3 RCTs included; 528 patients) Gad 2012 Marcoux 1997 Moini 2012 Analysis 1.6.1	Surgery versus diagnostic laparoscopy	Pregnancy rate	See Summary of findings table	There is moderate quality evidence that laparoscopic surgery increases viable intrauterine pregnancy rates confirmed by ultrasound compared to diagnostic laparoscopy only.	
(Hodgson, *et al.*, 2020)	systematic review and network meta-analysis of RCTs	Women with endometriosis confirmed by laparoscopy with associated infertility. 36 trials in the systematic review and 26 trials reporting on 2,245	Different interventions, including surgery	Pregnancy rate	Network meta-analysis showed that compared with placebo, surgical laparoscopy alone (OR 1.63; 95% CI 1.13-2.35) or GnRH agonist alone (OR 1.68; 95% CI, 1.07-2.46) results in higher odds of pregnancy.	The most important conclusion is that more RCTs are needed to clarify the relative effectiveness of treatments for endometriosis-related infertility, ideally comparing interventions to existing	

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
		women with endometriosis-related infertility in the network meta-analysis.			The evidence on the other interventions versus placebo or on the secondary outcomes including live birth, miscarriage, and adverse events is insufficient.	recommended interventions such as surgical laparoscopy. In addition, further RCTs comparing IVF and IUI to other treatments are essential.	
(Jin and Ruiz Beguerie, 2014)	Review	Infertility associated with endometriosis (6 controlled trials included; 4 minimal/mild endometriosis + 2 moderate/severe endometriosis) 2 randomized studies, 4 non-randomized Marcoux et al 1997 Parazzini 1991 Chang et al 1997 Nowroozi et al 1987 Seiler et al 1986 Milingos et al 1999	Surgery Comparators: (1)no treatment; (2) placebo; (3) medical therapy; and (4) non-laparoscopic surgical treatment.	live birth rate clinical pregnancy rate fetal losses surgical complications	Clinical pregnancy rate: RR 1.44 (95% CI 1.24±1.68, p < 0.01). (5 studies - 933 participants) RCT data; RR of 1.44 (95% CI 1.06±1.95) Non-randomized trials ; RR of 1.45 (95% CI 1.45±1.71). LBR: RR : 1.52 (95% CI 1.26±1.84, p < 0.01) favoring laparoscopic surgery. (4 studies - 741 participants) Fetal loss: RR of 1.01 (95% CI 0.56±1.79) No difference between lap surgery and diagn lap (4 RCTS, n=310)		
ENDOMETRIOMA							
(Dan and Limin, 2013)	Systematic review and meta-analysis	Endometrioma Alborzi et al 2004 Alborzi et al. 2007 Beretta et al. 1998 Carmona et al. 2011 Pados et al. 2010 Tsolakidis et al. 2010 Var et al. 2011	Cystectomy vs. fenestration/coagulation (2 studies) Cystectomy vs. laser vaporization (1 study)	Pregnancy rate Changes in AFC / AMH	Cystectomy vs. fenestration/coagulation PR cyst: 25/41 PR Fen/Co : 11/47 RR 2.64 (95% CI 1.49-4.69) Cystectomy vs. laser vaporization PR cyst : 5/26 PR laser; 5/24 RR 0.92 (95% CI 0.30-2.80) Changes in AFC Two studies reported a decreased AFC in cystectomized ovaries. Changes in AMH Concentrations Changes in AMH concentrations were only reported in one study. In this study, the decrease in the AMH concentration after surgery was found to be more	the findings from our meta-analysis indicate that laparoscopic cystectomy significantly reduces the rate of recurrent symptoms and the recurrence of endometrioma, and increases the rate of pregnancy compared with fenestration/coagulation and laser ablation (all but the rate of pregnancy) for treatment of endometrioma.	

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
					pronounced with cystectomy compared with the 'three-stage procedure'.		
(Candiani, *et al.*, 2020)	Comparative study	142 patients with symptomatic endometriomas.	laparoscopic stripping technique (Group 1) or cyst vaporization with CO2 fiber laser (Group 2) 39 women in Group 1 (53.4%) and 39 women in Group 2 (56.5%) desired to conceive after surgery 3 patients (7.7%) in Group 1 became pregnant following donor-IVF and were excluded.	pregnancy rates (+ predictors of pregnancy)	Pregnancy rate (NC/MAR) Cyst; 72.2% Laser; 74.3% SPR Cyst: 20/36 (55.5%) Laser: 14/39 (35.9%) Independent predictors for pregnancy Age at the time of surgery HR 0.86 (0.78-0.96) Duration of infertility HR 0.80 (0.69-0.92)	comparable probabilities of postoperative pregnancy in the 2 study groups. Women treated with CO2 laser vaporization were 30% less likely to be pregnant spontaneously. Tthese women had higher AFC and AMH levels following surgery compared with those who had surgical excision of the cyst. .	
(Alborzi, *et al.*, 2019)	Review	Endometrioma 2000 to 2018, Bila et al 2018 Alborzi 2007 Bussaca 2006 Alborzi 2004 Pubuccu 2004 Demirol 2006 Fisch 2004 Suganum 2002	Surgery vs surgery+ART/ aspiration ± sclerotherapy + ART / ART alone	clinical pregnancy rates (8 studies)	PR in surgery only group; 43.8% (CI: 22.5-66.4); Not different vs other groups	The most commonly used methods were surgery + ART (43.94%), aspiration ± sclerotherapy + ART (25.67%), ART alone (15.91%), and surgery (14.46%)	
DEEP ENDOMETRIOSIS							
(Iversen, *et al.*, 2017)	Review	bowel DIE 4 Retrospective observational studies + 3 prospective studies + 2 controlled studies No meta-analysis	Surgery Retrospective observational studies: Laparoscopic segmental OR En bloc resection OR Local discoid excision. prospective studies: Laparoscopic colorectal resection OR Disc excision using the Rouen technique.	Spontaneous pregnancy rate	Retrospective observational: Total 415 patients, 136 with desire for pregnancy Spontaneous PR; 49% Prospective studies Total n=4901, 184 desiring pregnancy Spontaneous PR; 21% Controlled studies: Stepnieuwska 2009 : Spontaneous PR improved after surgery for bowel endometriosis Ballester2017: (IVF pregnancies only)	The majority of observational studies in the present review indicate a postoperative SPR of 40% to up to more than 60%. The highest value was reported from a large volume, single-surgeon center, with a low risk of grade C leakage and of major complications in general. These results may not be generally applicable but they reflect that DIE surgery should be restricted to subspecialized centers where results are monitored to provide proper data for the decision process. Taken together, available data are	

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
						of poor quality but it seems that surgery for bowel DIE does improve SPR.	
(Meuleman, *et al.*, 2011b)	SR	3894 patients who underwent surgical treatment for DIE with colorectal involvement Fertility assessed in 28 patients who actively wanted to become pregnant after surgery and who had either primary (n = 23 of 28, 82%) or secondary infertility (n = 5of 28, 18%).		Fertility outcome after surgery	13 out of 28 patients became pregnant - pregnancy rate of 46%) during a median follow-up period of 27 months (range: 16–40 months) after surgery - cumulative pregnancy rate (life table analysis) of 7, 29 and 47% after 1, 2 and 3 years, resp One patient was pregnant twice, and one patient had miscarriage. Pregnancy occurred spontaneously (n = 8) or after IVF (n = 5) in patients with either primary (10 of 13) or secondary (3 of 13) infertility.		Pain data see Question II.3
(Vercellini, *et al.*, 2012a)	Review	rectovaginal and rectosigmoid endometriosis (infertile before surgery) Studies between 2005 and 2011 11 selected studies,	Surgery	spontaneous pregnancy rate	<u>mean post-operative conception rate (independent of pre-op fertility status and IVF performance)</u> 39% (95% CI 35–43%; 223/571) <u>mean post-operative conception rate (infertile and spontaneous PR)</u> 24% (95% CI20–28%; 123/510) (OR 0.50, 95% CI 0.38–0.65%)	Patients' selection significantly influences the estimate of the effect of rectovaginal endometriosis excision on infertility. This should be carefully taken into consideration at preoperative counselling	

EVIDENCE TO RECOMMENDATIONS - peritoneal endometriosis

The evidence (and its quality)	Laparoscopic surgery was found to increase (natural) viable intrauterine pregnancy rates (Bafort 2020) in a review including trials of rASRM stage I/II endometriosis. No evidence on live birth rates. Quality of evidence: ⊕⊕◯◯ (downgraded from the review as indirect evidence for peritoneal endometriosis)
Balance between desirable and undesirable outcomes	The benefit with regards to the impact on LBR/Pregnancy rate (and possible additional benefit with regards to pain outcomes) versus the complications of surgery

Balance between different outcomes	Operative laparoscopy was found to have a positive effect on ongoing pregnancy. Complications are as described in the section on pain management. In line with the recommendation of surgery as on option for pain relief, it was agreed that laparoscopy could be offered as an option for endometriosis-associated infertility, but also to specify that data are limited to ongoing pregnancy
Patient values and preference	There are no data supporting a single treatment pathway applicable for all women with endometriosis. As such, treatment options are presented as options, with room for consideration of individual patient values and preferences
Resource use, equity, acceptability and feasibility	Surgery is considered acceptable and feasible, although it may require more resources compared to medical treatment
RECOMMENDATION	**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.**

EVIDENCE TO RECOMMENDATIONS - endometrioma

The evidence (and its quality)	No comparative studies evaluating LBR/PR after surgery versus no surgery were found. Before and after studies suggest a positive effect of surgery on pregnancy rates. Quality of evidence: ⊕◯◯◯ (indirect evidence, observational data only)
Balance between desirable and undesirable outcomes	The benefit with regards to the impact on LBR/Pregnancy rate (and possible additional benefit with regards to pain outcomes) versus the complications of surgery
Balance between different outcomes	Operative laparoscopy was found to have a positive effect on pregnancy. Complications are as described in the section on pain management. It was decided to formulate a weak recommendation for surgery with clarification on the lack of data from comparative studies.
Patient values and preference	There are no data supporting a single treatment pathway applicable for all women with endometriosis. As such, treatment options are presented as options, with room for consideration of individual patient values and preferences
Resource use, equity, acceptability and feasibility	Surgery is considered acceptable and feasible, although it may require more resources compared to medical treatment
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.**

EVIDENCE TO RECOMMENDATIONS - deep endometriosis

The evidence (and its quality)	No compelling evidence for a benefit of surgery with regards to LBR/PR. Quality of evidence: ⊕◯◯◯ (indirect evidence, observational data only)
Balance between desirable and undesirable outcomes	The benefit with regards to the impact on LBR/Pregnancy rate (and possible additional benefit with regards to pain outcomes) versus the complications of surgery
Balance between different outcomes	Surgery is DE is more often associated with complications. Only for a subgroup of patients with pain symptoms, laparoscopy may be considered a treatment option.

Patient values and preference	There are no data supporting a single treatment pathway applicable for all women with endometriosis. As such, treatment options are presented as options, with room for consideration of individual patient values and preferences
Resource use, equity, acceptability and feasibility	Surgery is considered acceptable and feasible, although it may require more resources compared to medical treatment
RECOMMENDATION	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.
GPP	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.

QUESTION III.3 WHICH PATIENTS NEED TREATMENT WITH ASSISTED REPRODUCTION TECHNOLOGY AFTER SURGERY?

NARRATIVE QUESTION

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Not applicable

INCLUDED REFERENCES (Narrative question)
(Adamson and Pasta, 2010, Tomassetti*, et al.*, 2020, Vesali*, et al.*, 2020)

EVIDENCE TO RECOMMENDATIONS

Not applicable

The GDG formulated the following 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.

QUESTION III.4 IS MEDICALLY ASSISTED REPRODUCTION EFFECTIVE FOR INFERTILITY ASSOCIATED WITH ENDOMETRIOSIS?

Intra-uterine insemination

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Tummon, *et al.*, 1997)	RCT	103 pts; 311 cycles. IUI – 53 pts; 127 cycles; No treatment – 50 couples; 184 cycles **Inclusion criteria**: 20-39 years old without any infertility factor and minimal or mild endometriosis diagnosed visually at laparoscopy in the previous 12 months (with or without treatment) **Exclusion criteria**: hormonal endometriosis therapy in the previous 6 months, ovulation induction in previous the 3 months, previous ovulation induction with exogenous gonadotropins	Ovarian stimulation + IUI vs no treatment	Live birth (LB)	LB – 11% per treatment cycle in IUI group and 2% per cycle in the no treatment group. OR of LB of 5.6 (1.8-17.4) in favor of ovarian stimulation + IUI.	Superovulation with IUI may be an appropriate beginning form of assisted reproduction for highly motivated individuals.	
(Nulsen, *et al.*, 1993)	RCT	119 couples Endo – 57 (11 of them with also male factor); Unexplained – 21; male – 20; other – 21 Minimal, mild and moderate endometriosis. Ablation or excision of endometriotic implants at the occasion of diagnostic laparoscopy.	Human menopausal gonadotropin/IUI, or IUI alone (timed by either urine LH monitoring or BBT) 11 cycles max	Cycle fecundity (rising HCG) Pregnancy outcome Cumulative pregnancy rates (PR)	Cycle fecundity (endo patients): HMG/IUI 15/57 (11.8%); IUI alone 2/96 (2.1%); RR5.1 (95% CI 1.1-22.5). Pregnancy outcome: miscarriage rate - 24.2%; multiple gestation rate - 18.2% For the entire group; no numbers per etiologic group) Cumulative PR for HMG/IUI (after 7 cycles): 80% for unexplained; 53% for endo patients; 48% for male infertility.	Human menopausal gonadotropin/IUI is more effective than IUI alone for the treatment of endometriosis, male factor infertility, and unexplained infertility	
(Omland, *et al.*, 1998)	Cohort study	n=168 Unexplained infertility (UI)- 119 Minimal endometriosis (E) – 49 Inclusion criteria and exclusion criteria clearly and correctly described (only cases with	Ovulation stimulation in both groups followed by AIH (IUI+IPI per cycle and, after 1994, two IUI per cycle).	Pregnancy rate	UI group – 40/119 (33.6%) E group – 8/49 (16.3%) [p<0.05)	Higher pregnancy rate and more implantations per cycle in cases of UI compared with infertility associated with peritoneal endometriosis	Two different regimens used for ovarian stimulation: CC+HMG/FSH or HMG/FSH alone.

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
		peritoneal endometriosis and no adhesions were included) Age distribution, duration of infertility and frequency of primary infertility – similar in both groups	One cycle of IAH				According to the authors they were randomly used for workload programming, but no detailed information is reported about the frequency of each one in each group.
(Werbrouck, *et al.*, 2006)	retrospective, controlled cohort study	107 pts; 259 treatment cycles. Endo – 58 pts, 137 cycles Unexplained infertility (UI) – 49 pts, 122 cycles **Inclusion criteria**: Minimal (n=41; 100 cycles) or mild (n=17; 37 cycles) endometriosis, surgically treated within 7 months before first cycle of IUI in the absence of any other infertility factor. Groups were similar except a significant lower duration of the infertility in the UI cases.	Ovarian stimulation with clomiphene citrate (CC) – 23 cycles) or gonadotrophins (236 cycles) plusIUI One to four treatment cycles per patient	Pregnancy rate (PR) Cumulative life-birth rate (CLBR) after 4 treatment cycles	PR per cycle: Endo – 20% (minimal – 21%, mild – 19%); Unexplained – 20.5%. CLBR: Endo I – 70.2%; endo II – 68.2; unexplained – 66.5% (NS)	The data suggest that ovarian stimulation and IUI shortly after laparoscopic excision of endometriosis is as effective as COH and IUI in patients with unexplained subfertility	
(van der Houwen, *et al.*, 2014)	Retrospective study	65 patients receiving 245 IUI treatment cycles	IUI with ovarian stimulation (IUI/OS) versus IUI without ovarian stimulation in the first three cycles followed by IUI with ovarian stimulation (IUI + IUI/OS)	Treatment outcomes, recurrences and complications	8 (40.0%) versus 7 (15.6%) ongoing pregnancies were accomplished in IUI/OS (n=20, 61 cycles) versus IUI + IUI/OS (n=45, 184 cycles). Preceding long-term pituitary down-regulation tended to result in a higher ongoing pregnancy rate (adjusted HR 1.8) and a higher chance of endometriosis recurrence (adjusted HR 2.3). 8 (40.0%) versus 16 (35.6%) recurrences of endometriosis complaints were reported in IUI/OS vs IUI + IUI/OS		
(Kim, *et al.*, 1996)	RCT	80 Ultralong protocol – 39 Long protocol (LP) – 41 Infertile patients with laparoscopic confirmation and staging of endometriosis. No other infertility factor. Two groups based in the protocol of GnRH agonist used for ovarian stimulation: Ultralong protocol – 39 cycles (39 patients): 19 with minimal	IUI in both groups 36-40 h after HCG. **Ultralong protocol (ULP)** - one dose of GnRH agonist (3.75 mg Decapeptyl) at the mid-luteal phase of the menstrual cycle; four weeks afterwards daily s.c. administration of 0.1	Clinical pregnancy rate (CPR). Pregnancy outcomes	CPR: 19/39 **(48.3%)** (ULP) vs 11/41 **(26.8%)** (LP) p<0.05). Pregnancy outcome: -spontaneous abortion 4/19 vs 2/11 (NS) - multiple pregnancies 3/19 vs 1/11 (NS) Comparison according to severity of endometriosis: - Minimal or mild endometriosis – CPR 9/19 vs 7/20 (NS);	No significant difference between the two groups of endometriosis I or II with respect to clinical pregnancy rate per cycle (47.4 versus 35.0%). In patients with stage III or IV endometriosis, the CPR per cycle was significantly higher in the ULP group - 50.0% (10/20) compared with 19.0% (4/21) in the LP group.	

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
		or mild, and 20 with moderate or severe endometriosis. Long protocol (LP) - 41 cycles (41 patients): 20 with minimal or mild, and 21 with moderate or severe endometriosis. Age distribution, duration of infertility, frequency of primary infertility, semen parameters and endocrine profile – similar in both groups	mg Decapeptyl for at least 2 weeks. **Long protocol (LP) -** Daily s.c. administration of 0.1 mg Decapeptyl initiated from the mid-luteal phase of the menstrual cycle. After 14 days of administration evaluation of the pituitary desensitization. After confirmation of pituitary desensitization, HMG and HFSH 150IU of each for 4 days and only HMG in individualized dosage thereafter. GnRH agonist was maintained in the LP group until HCG administration.		- Moderate or severe endometriosis – CPR 10/20 **(50%)** vs 4/21 **(19%)** ($p<0.05$)	A simplified ULP of GnRHa could give better chances of achieving pregnancy in endometriosis patients undergoing assisted reproductive technologies and this protocol may be more useful in patients with an advanced stage of endometriosis.	

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	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 (Tummon, et al., 1997) and effective in increasing biochemical pregnancy rate, compared to IUI alone (Nulsen, et al., 1993) Quality of evidence: ⊕◯◯◯ (small single studies)
Balance between desirable and undesirable outcomes	LBR/Pregnancy rate versus side effects of treatment (IUI). Time to pregnancy is another factor to be considered
Balance between different outcomes	IUI with ovarian stimulation seems to be an effective treatment for increasing pregnancy rates, while not associated with signicifant side effects
Patient values and preference	No data

Resource use, equity, acceptability and feasibility	IUI (with ovarian stimulation) is an acceptable and feasible treatment option for fertility issues. It generally has a smaller impact on resources, compared other treatment options (surgery, ART)
RECOMMENDATION	**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.**

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	In patients with moderate to severe endometriosis, the benefit of IUI is unclear as only retrospective low evidence data are available. IUI with ovarian stimulation seems to be more efficient that IUI only (van der Houwen et al., 2014). Quality of evidence: ⊕◯◯◯
Balance between desirable and undesirable outcomes	LBR/Pregnancy rate versus side effects of treatment (IUI). Time to pregnancy is another factor to be considered
Balance between different outcomes	In infertile women with AFS/ASRM stage III/IV endometriosis with tubal patency, there is insufficient evidence to recommend or discourage IUI (weak recommendation). Based on the higher efficiency for IUI with ovarian stimulation, this is weakly recommended
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	IUI (with ovarian stimulation) is an acceptable and feasible treatment option for fertility issues. It generally has a smaller impact on resources, compared other treatment options (surgery, ART)
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.**

Assisted reproduction

Summary of Findings Table

Not applicable, no studies comparing ART with no treatment or other treatments

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Harb, *et al.*, 2013)	systematic review and meta-analysis	Endometriosis 27 observational studies comprising 8984 women.	IVF	IVF outcome (stage I/II or III/IV) versus controls) - Fertilisation rate - Implantation rate CPR	fertilisation rates were reduced in stage I/II of endometriosis (relative risk [RR] = 0.93, 95% confidence interval [95% CI] 0.87–0.99, P = 0.03). There was a decrease in the implantation rate (RR = 0.79, 95% CI 0.67–0.93, P = 0.006) and clinical pregnancy rate (RR = 0.79, 95% CI 0.69–0.91, P = 0.0008)	The presence of severe endometriosis (stage III/IV) is associated with poor implantation and clinical pregnancy rates	

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
					in women with stage III/IV endometriosis		
(Hamdan, *et al.*, 2015b)	systematic review and meta-analysis	36 retrospective observational studies (n=29,454)	IVF	live birth rate (endometriosis vs no endometriosis) CPR mean number of oocytes retrieved per cycle subgroup analysis STAGE I/II vs no endometriosis Stage III/IV vs no endo	(OR 0.94,95% CI 0.84–1.06, 13 studies,12,682 patients, I2=35%) Lower (OR 0.78, 95% CI 0.65–0.94, 24 studies, 20,757 patients, I2=66%) Lower (mean difference 21.98, 95% CI 22.87 to 21.09, 17 studies, 17,593 cycles, I2=97%) All outcomes comparable Lower LBR (OR 0.77, 95%CI 0.64–0.92, 8 studies, 3,849 pts, I2=0%) lower CPR (OR 0.60, 95%CI 0.44–0.81,15 sts, 9,471 pts, I2=71%) lower mean number of oocytes retrieved per cycle (MD 21.76, 95% CI 22.73 to 0.79, 14 cycles, 9,172 patients, I2=92%)	women with endometriosis undertaking ART have a similar live birth rate, a lower clinical pregnancy rate, and lower mean number of oocytes retrieved per cycle when compared with those without endometriosis.	
(Senapati, *et al.*, 2016)	Population-based retrospective cohort study	347,185 autologous fresh and frozen assisted reproductive technology cycles Although cycles of endometriosis patients constituted 11% of the study sample, the majority (64%) reported a concomitant diagnosis, with male factor (42%), tubal factor (29%), and diminished ovarian reserve (22%) being the most common.			Endometriosis, when isolated or with concomitant diagnoses, was associated with lower oocyte yield compared with those with unexplained infertility, tubal factor, and all other infertility diagnoses combined. Women with isolated endometriosis had similar or higher LBR compared with those in other diagnostic groups. However, women with endometriosis with concomitant diagnoses had lower implantation rates and LBR compared with unexplained infertility, tubal factor, and all other diagnostic groups.	Endometriosis is associated with lower oocyte yield, lower implantation rates, and lower pregnancy rates after IVF	
(Muteshi, *et al.*, 2018)	retrospective cohort study	Women with endometriosis (n = 531) and women with unexplained subfertility (n = 737) undergoing a first cycle of IVF-ET		LBR	Women with endometriosis : 24% less likelihood of a live birth [OR 0.76 (95% CI, 0.59–0.98) P = 0.035]. This effect became more apparent with increasing severity of endometriosis. Using multivariable logistic regression analysis, the trend for lower LBR remained but did not reach statistical	Endometriosis decreases live birth rate in women undergoing IVF-ET treatment, particularly with increasing severity of the disease.	

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
				MPR oocytes retrieved / blastocyst transfer rate / implantation rate	significance [adjusted OR 0.76 (95% CI 0.56–1.03), P = 0.078]. Similar singleton live birth with double ET compared to single ET [OR 1.38 (95% CI 0.73–2.62), P = 0.32 and OR 3.22 (95% CI 1.7–6.05), P = 0.0003, resp]. Women with endometriosis had fewer oocytes retrieved [(10.54 (95% CI 10.13–0.95) and 9.15 (95% CI 8.69–9.6), resp], lower blastocyst transfer [OR 0.24 (95% CI 0.12–0.5), P = 0.0001] and a significantly reduced implantation rate [OR 0.73 (0.58–0.92), P = 0.007].		
(Murta, *et al.*, 2018)	retrospective study	27,294 cycles of IVF/ICSI Endometriosis (n = 1749) Control (n = 5747) (tubal factor or unexplained infertility)		live birth rate (number of live births per pregnancy). The secondary outcomes were implantation and clinical pregnancy (gestational sac with heartbeat) rates.	higher pregnancy rates, per cycle initiated and per embryo transfer and higher live birth rate in the endometriosis group. LBR: 85.4% vs 79.2% (<0.001) PR/initiated cycle: 41.6% vs 30.5% (<0.001) The mean number of retrieved oocytes was higher in the control group, but the mean number of metaphase II oocytes was similar. Fertilization rate and transfer rate were higher in the control group.	endometriosis does not affect the outcome of patients subjected to IVF/ICSI and although patients with endometriosis present lower number of oocytes and higher cancelation rate, these shortcomings do not reduce pregnancy and live birth rates.	
(Alshehre, *et al.*, 2020).	Review	women with endometrioma versus controls Controls = women without endometrioma and/or tubal or male-factor infertility 8 studies included	ART (IVF/ICSI)	CPR, IR and LBR number of oocytes / MII oocytes gonadotrophin dose and duration total number of embryos / high-quality embryos	CPR, IR and LBR: no difference number of oocytes: WMD -2.25; 95%CI 3.43 to - 1.06 number of MII oocytes: WMD -4.64; 95%CI 5.65 to -3.63 gonadotrophin dose and duration: no difference total number of embryos / high-quality embryos: no difference	number of oocytes/ MII oocytes retrieved were significantly lower in women with endometrioma	

INCLUDED AS BACKGROUND INFORMATION
(Danhof, *et al.*, 2018, Diamond, *et al.*, 2015)

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	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 extent of the disease might play a role with stage III-IV endometriosis potentially decreasing the live birth rate. Quality of evidence: ⊕⊕◯◯ (observational data only)
Balance between desirable and undesirable outcomes	Efficacy of treatment versus side effects (including invasiness and costs)
Balance between different outcomes	ART seems to be as efficient in women with endometriosis as in women with other fertility issues. There is no evidence on whether IUI or ART is superior in women with endometriosis, but in a specific subgroup (specified in the recommendation), IUI is not the appropriate treatment and ART can be performed.
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	ART is an acceptable and feasible treatment option for fertility issues, although it may be associated with significant costs.
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.**

Assisted reproduction – type of protocol

Summary of Findings Table

No applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Pabuccu, *et al.*, 2007)	RCT	246 pts submitted to ICSI: Group I) mild-to-moderate endometriosis (n= 98); Group II) previous ovarian surgery for endometrioma and no present endometrioma(n=81); Group III) present endometrioma and no history of previous surgery (n=67). Only fresh cycles. **Exclusion criteria**: Presence of endometrioma after surgery, endometriosis III-IV without endometrioma, hydrosalpinx, tuberculosis, male factor. The basal characteristics of patients were similar within each group	Randomization within each group for long protocol with agonist (triptorelin) started in the luteal phase or protocol with antagonist (cetrorelix): Group I - GnRH- a=48; GnRH ant=50); Group II - GnRH- a=41; GnRH ant=40); Group III - GnRH- a=33; GnRH ant=34); Rec FSH for Ovarian stimulation (COH). Randomization list generated by computer.	Parameters of ovarian response, ICSI cycle results (Implantation rate (IR) - Clinical pregnancy rate (PR))	In groups II and III several small and clinical not relevant differences in parameters of ovarian response to COH. GnRH-a vs GnRH antag - Group I (all results NS): IR – 18.2% vs 15.4%; PR – 31.2% vs 31% Group II: IR – 22.6% vs 15.9%; PR – 39% vs 27.5%; Group III: IR – 14.8% vs 12.5%; PR – 24.2% vs 20.5%.	Considering the implantation and clinical pregnancy rates, COH with both GnRH antagonist and GnRH-a protocols may be equally effective in patients with mild-to-moderate endometriosis and endometrioma who did and did not undergo ovarian surgery.	I feel the author's conclusion too much affirmative: IR and PR were always lower in antagonist cycles and there was no sample size calculation. "…COH with GnRH antagonist protocol was not found to be inferior to GnRH-a protocol in …" would be ö more accurate.
(Rodriguez-Purata, *et al.*, 2013)	Observational, retrospective analysis	1180 patients with endometriosis confirmed by ultrasound or surgery (AFS grades I–IV)	standard controlled ovarian hyperstimulation (COH) and GnRHa (919 cycles) or GnRHant. (261 cycles)	pregnancy rate (PR) per cycle	raw PRs: per cycle being 41.8% with the GnRHa and 23.4% for the GnRHant; and 44.3% and 27% per ET, respectively. Subgroups based on propensity score (PS)		
(Bastu, *et al.*, 2014)	retrospective study	86 stage III to IV who had undergone laparoscopic resection surgery for endometrioma	ovarian stimulation with a long GnRH-a protocol (n=44), and those who had ovarian stimulation with a GnRH- ant protocol (n = 42).	PR	There were no significant differences in positive hCG PR (25% vs 21.4%; P = .269) and ongoing PR per patient (20.5% vs 19.1%; P =.302) between the 2 protocols.		
(Kolanska, *et al.*, 2017)	Retrospective analysis	284 COH cycles –165 with GnRH-agonist protocol (GnRH-agonist group) and	GnRH-agonist versus GnRH-antagonist	PR – LBR per started cycle	After fresh ET PR and LBR were higher with the GnRH-agonist		

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
		119 with GnRH-antagonist protocol (GnRH-antagonist group) – in 218 women, with endometriosis		PR – LBR analysis per cycle with ET	protocol (25% vs. 13%, P = 0.02 and 18% vs. 8%, P = 0.04, resp). Per cycle with ET, PR was similar in both groups while the LBR was higher in the GnRH-agonist group (29% vs. 17%, P = 0.053 and 22% vs. 10%, P = 0.02, resp). No difference was observed between the groups with freeze-thaw embryo transfer. Subgroup analysis (endometrioma alone, DE with and without endometrioma, endometriosis with and without adenomyosis) revealed no difference between the groups for either PR or LBR		
(Drakopoulos, *et al.*, 2018)	retrospective cohort	386 endometriosis patients (rAFS classified) stage I–II: 42 agonist – 75 antagonist stage III–IV: 143 agonist – 126 antagonist	IVF/ICSI - long GnRH agonist or GnRH antagonist protocol	b-hCG positive, clinical pregnancy, and LBR	endometriosis stage I–II: tendency toward higher b-hCG positive, clinical pregnancy, and LBR (42.8% vs. 26.7%; p¼.07) in favor of GnRH agonist use. endometriosis stage III–IV, no differences were observed between agonist and antagonist cycle in any of the pregnancy outcomes.		

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	No overall difference in LBR in GnRHa versus GnRHanta protocols (Pabuccu, et al., 2007, Rodriguez-Purata et al., 2013, Bastu et al., 2014, Kolanska, et al., 2017, Drakopoulos, et al., 2018). Quality of evidence: ⊕◯◯◯ (observational data only, small studies, different interventions/outcomes)
Balance between desirable and undesirable outcomes	Efficacy versus costs/side effects
Balance between different outcomes	No evidence of superiority of any of the protocols
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	ART is an acceptable and feasible treatment option for fertility issues, although it may be associated with significant costs.
RECOMMENDATION	**A specific protocol for ART in women with endometriosis cannot be recommended. Both 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.**

Assisted reproduction – safety

Summary of Findings Table

No applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Somigliana, *et al.*, 2019)	Review	Sixteen studies Endometriosis	IVF	Complications	No meta-analysis	(i) IVF does not worsen endometriosis-related pain symptoms (moderate quality); (ii) IVF does not increase the risk of endometriosis recurrence (moderate quality evidence); (iii) the impact of IVF on ovarian endometriomas, if present at all, is mild (low quality); (iv) IUI may increase the risk of endometriosis recurrence (low quality evidence); DE might progress with ovarian stimulation (very low quality evidence).	
(Benaglia, *et al.*, 2008)	Cohort study	119 pts 214 oocyte retrievals Women with one or more ovarian endometriomas who underwent oocyte retrieval	Oocyte retrieval in the context of IVF/ICSI	Frequency of pelvic abscess	0.0 pelvic abscess (95% CI – 0.0-1.7%)	In women with endometriomas who are selected for IVF, the risk of developing pelvic abscess after oocyte retrieval is very low.	Only 6 cases (3%) of accidentally punctured endometriomas ; Antibiotic prophylaxis during 3 days in these patients

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	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. Quality of evidence: ⊕⊕⊕◯ The use of antibiotic prophylaxis at the time of oocyte retrieval in women with endometriomas seems reasonable (no evidence) and is recommended as a good practice point.
Balance between desirable and undesirable outcomes	Impact of ART on endometriosis recurrence versus benefits towards achieving pregnancy
Balance between different outcomes	ART was not associated with increased endometriosis recurrence rate and should not be withheld from women with endometriosis as it may increase their chances of a pregnancy
Patient values and preference	No data

Resource use, equity, acceptability and feasibility	Not applicable for this question
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.
GPP	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.

QUESTION III.5 ARE MEDICAL THERAPIES EFFECTIVE AS AN ADJUNCT TO MAR FOR ENDOMETRIOSIS-ASSOCIATED INFERTILITY?

Summary of Findings Table

III.5 Medical therapies (GnRH agonist therapy) + IVF compared to IVF only for increasing pregnancy rates in women with endometriosis

Patient or population: increasing pregnancy rates in women with endometriosis
Setting:
Intervention: Medical therapies (GnRH agonist therapy) + IVF
Comparison: IVF only

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with IVF only	Risk with Medical therapies (GnRH agonist therapy) + IVF				
Live birth rate	355 per 1,000	**171 per 1,000** (92 to 309)	**RR 0.48** (0.26 to 0.87)	147 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	Based on Georgiou et al. 2019
Clinical Pregnancy Rate	331 per 1,000	**374 per 1,000** (301 to 467)	**RR 1.13** (0.91 to 1.41)	552 (6 RCTs)	⨁⨁◯◯ LOW [c,d]	Based on Georgiou et al. 2019
Miscarriage rate	46 per 1,000	**21 per 1,000** (5 to 88)	**OR 0.45** (0.10 to 2.00)	208 (2 RCTs)	⨁◯◯◯ VERY LOW [d,e,f]	Based on Georgiou et al. 2019
Multiple pregnancy rate	74 per 1,000	**11 per 1,000** (2 to 43)	**OR 0.14** (0.03 to 0.56)	208 (2 RCTs)	⨁◯◯◯ VERY LOW [d,e,f]	Based on Georgiou et al. 2019
Pregnancy	341 per 1,000	**375 per 1,000** (274 to 487)	**OR 1.16** (0.73 to 1.84)	272 (1 RCT)	⨁⨁◯◯ LOW [d,g]	Kaponis et al. 2020

Explanations
a. Single unpublished study
b. Cannot be assessed
c. Inconsistent results across individual studies
d. Imprecision detected
e. Based on 2 studies of which 1 unpublished
f. Limited number of events
g. Single study

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Georgiou, *et al.*, 2019)	Cochrane review	Endometriosis	long-term GnRH agonist therapy (minimum 3 months) versus no pretreatment before IVF/ICSI	LBR Complication rate PR Multiple pregnancy rate Miscarriage rate	We are uncertain whether long-term GnRH agonist therapy affects the live birth rate (RR 0.48, 95% CI 0.26 to 0.87; 1 RCT, n = 147; I2 not calculable; very low-quality evidence) or the overall complication rate (Peto OR 1.23, 95% CI 0.37; to 4.14; 3 RCTs, n = 318; I2 = 73%; very low-quality evidence) compared to standard IVF/ICSI. Further, we are uncertain whether this intervention affects the clinical pregnancy rate (RR 1.13, 95% CI 0.91 to 1.41; 6 RCTs, n = 552, I2 = 66%; very low-quality evidence), multiple pregnancy rate (Peto OR 0.14, 95% CI 0.03 to 0.56; 2 RCTs, n = 208, I2 = 0%; very low-quality evidence), miscarriage rate (Peto OR 0.45, 95% CI 0.10 to 2.00; 2 RCTs, n = 208; I2 = 0%; very low-quality evidence), mean number of oocytes (MD 0.72, 95% CI 0.06 to 1.38; 4 RCTs, n = 385; I2 = 81%; very low-quality evidence) or mean number of embryos (MD -0.76, 95% CI -1.33 to -0.19; 2 RCTs, n = 267; I2 = 0%; very low-quality evidence).		See SOF table
(Kaponis, *et al.*, 2020)	RCT	400 infertile women with mild endometriosis, ~~200 women with tubal factor infertility.~~	GnRH-a for 3 months before an IVF attempt versus IVF without GnRH-a				See SOF table
(de Ziegler, *et al.*, 2010)			oral contraceptives before IVF group 1 : OC before ART continuously for 6 to 8 weeks group 2 : no OC	CPR (group 1 vs group 2)	Stage I/II; 48.1% versus 23.6) Stage III/IV; 37.9 vs 21.2 Endometrioma: 41.4 vs 12.9 ($p<0.01$) 6 to 8 weeks of OC treatment before ART did not further alter the already compromised ovarian response to COH encountered in women with endometriomas. The amount of gonadotropin required in the women with endometriomas of group 1 who were pretreated with OC for 6 to 8 weeks (3,163 ± 1,350 IU) actually tended to be lower than in the women of group 2 who did not receive OC treatment (3,677 ± 1,590 IU).	Our findings suggest that 6 to 8 weeks of OC treatment before ART may be as effective as suppressing ovarian function with a GnRH agonist for 3 to 6 months for optimizing ART outcome in endometriosis	
(Cao, *et al.*, 2020).	Review and meta-analysis	infertile women with endometriosis. 21 articles included; 7 RCTs + 14 cohort studies	different GnRH agonist protocols (short, long, ultralong)	CPR IR FR	based on evidence from RCTs: Higher CPR with ULP in III-IV endometriosis: (RR 2.04, 95%CI 1.37 to 3.04; 2 RCTs; 152 patients) Based on RCTs + observational studies : no diff	This study suggests that the GnRH-a ultra-long protocol can improve the clinical pregnancy rate of the patients with stages III–IV endometriosis in RCTs. Although it is generally believed that the results of RCT are more reliable, the conclusions of the non-RCT	

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
						studies cannot be easily neglect, which let us draw conclusions more cautious.	
(Tamura, *et al.*, 2019).	RCT	68 women with stage III/IV + infertility (ovarian endometrial cyst < 4 cm)	dienogest (DNG) during 12 weeks before IVF (n=33) vs no pre-treatment (n=35) DNG was administered orally every day for 12 weeks prior to the conventional IVF-ET cycle	cumulative pregnancy rate and live birth rate Numbers of growing follicles, retrieved oocytes, fertilized oocytes, and blastocysts Fertilization/blastocyst rates	The numbers of growing follicles, retrieved oocytes, fertilized oocytes, and blastocysts: significantly lower in the DNG group Fertilization and blastocyst rates: significantly lower in the DNG group cumulative pregnancy rate and live birth rate: significantly lower in the DNG group	Administering DNG treatment just before IVF-ET did not provide any benefits to improve the clinical outcomes for infertile women with endometriosis.	
(Guo, *et al.*, 2020).	non-inferiority RCT	450 women with stage III/IV patients with ovarian advanced endometriosis but normal ovarian functions.	MPA + hMG (n=150) dydrogesterone + hMG (n=150) progesterone + hMG (n=150)	number of oocytes retrieved FR CPR	MPA + hMG group: higher nr of oocytes (9.3 ± 5.7 vs. 8.0 ± 4.5 vs. 7.8 ± 5.2, P = 0.021). No diff in FR/CPR	three different progestins protocols are equivalent in terms of pregnancy outcomes for women with advanced endometriosis	
(Barra, *et al.*, 2020).	retrospective study	151 endometriosis (Imaging diagnosis) and a previous failed IVF cycle	3 months DNG (2 mg/daily) pre-treatment prior to IVF (n=88) no pre-treatment (n=63)	cumulative implantation clinical pregnancy rate live birth rate diameter of endometriomas oocytes retrieved 2PN embryos blastocysts	CIR: 39.7% vs 23.9% - p=0.049 CPR : 33.3% vs 18.2% - p=0.037 LBR : 28.6% vs 14.8%, p=0.043 All increased with pretreatment In DNG group: largest diameter of endometriomas significantly decreased (P < 0.001). significantly increased number of oocytes retrieved (P = 0.031), 2PN embryos (P = 0.039) and blastocysts (P = 0.005) - in women with endometriomas ≥4 cm.)	in patients with endometriosis, IVF outcomes can be improved by pretreatment with DNG, in particular in women with larger endometroimas	

INCLUDED AS BACKGROUND INFORMATION
(Dicker, *et al.*, 1992, NCT01581359, Sallam, *et al.*, 2006, Tomassetti, *et al.*, 2021).

EVIDENCE TO RECOMMENDATIONS - GnRHa

The evidence (and its quality)	Based on the Cochrane review (Georgiou, *et al.*, 2019) (with limitations) the merit of 3–6 months GnRH agonist administration to women with endometriosis prior to ART compared to no pre-treatment is uncertain. Quality of evidence: ⊕◯◯◯
Balance between desirable and undesirable outcomes	Benefits with regards to LBR/pregnancy versus side effects of medical treatment
Balance between different outcomes	With uncertain benefit, the administration of GnRH agonist prior to ART treatment cannot be recommended. GnRH agonists have significant side effects
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	The costs and availability vary between the different interventions and between different countries/regions. No conclusion can be drawn, and it was suggested to consider costs and availability in shared decision making.
RECOMMENDATION	**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.**

EVIDENCE TO RECOMMENDATIONS – COC/progestogens

The evidence (and its quality)	The data concerning the use of COC or progestogens as a pre-treatment before ART for improving ART outcomes are very limited and do not allow to draw any conclusion. Quality of evidence: ⊕◯◯◯
Balance between desirable and undesirable outcomes	Benefits with regards to LBR/pregnancy versus side effects of medical treatment
Balance between different outcomes	With uncertain benefit, the administration of COC/progestogens prior to ART treatment cannot be recommended. There is also no evidence of a negative effect on pregnancy rate/LBR, and as COC is used in some centres/countries for planning purposes, it was decided to formulate a weak recommendation against COC/progestogens with the specific aim of increasing live birth rates
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	The costs and availability vary between the different interventions and between different countries/regions. No conclusion can be drawn, and it was suggested to consider costs and availability in shared decision making.
RECOMMENDATION	**There is insufficient evidence to recommend prolonged administration of the COC/progestogens as a pre-treatment to ART to increase live birth rates.**

QUESTION III.6 ARE SURGICAL THERAPIES EFFECTIVE AS AN ADJUNCT PRIOR TO MAR FOR ENDOMETRIOSIS-ASSOCIATED INFERTILITY?

Peritoneal endometriosis

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Opoien, *et al.*, 2011)	retrospective cohort study	minimal to mild endometriosis	First IVF cycle after Complete diathermy (n=399) or Diagnostic laparoscopy (n=262)	PR/initiated cycle LBR/initiated cycle	40.1 (160/399) after diathermy vs 29.4 (77/262) after no treatment (p<0.005) 27.6 (110/399) versus 20.6 (54/262) (p<0.05)	In cases of ASRM stages I and II endometriosis, complete elimination of endometriotic lesions and associated adhesions prior to IVF/ICSI was associated with improved LBR as well as a shorter time to first pregnancy.	
(Hamdan, *et al.*, 2015b)	systematic review and meta-analysis	36 retrospective observational studies (n=29,454) women with surgically treated stage I/II endometriosis	IVF	live birth rate / CPR / mean number of oocytes retrieved per cycle	<u>subgroup analysis</u> <u>STAGE I/II vs no endometriosis</u> All outcomes comparable <u>Surgically treated STAGE I/II vs no endometriosis</u> LBR: OR 0.88, 95%CI 0.76 to 1.02, 4 studies, 3492 patients (no diff) CPR: OR 0.69; 95%CI 0.50 to 0.96; 9 studies; 4888 patients (lower) mean number of oocytes : MD 22.37; 95%CI 23.55 to 21.20; 11 studies; 3909 cycles (lower)		

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	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 (Opoien, *et al.*, 2011). Indirect evidence from (Hamdan, *et al.*, 2015b). Quality of evidence: ⊕⊕◯◯
Balance between desirable and undesirable outcomes	Benefits with regards to LBR/pregnancy should be weight against possible surgical complications. There are reassuring data with regards to the complication rate associated with surgery for endometriosis (Bafort, *et al.*, 2020a, Byrne, *et al.*, 2018b, Chapron, *et al.*, 1998)
Balance between different outcomes	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.
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	Surgery is considered acceptable and feasible, although it may require more resources compared to some other treatment options
RECOMMENDATION	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.

Endometrioma - Surgery + IVF compared to IVF only

Summary of Findings Table

III.6a Surgery + IVF compared to IVF only for increasing pregnancy rates in women with endometrioma

Patient or population: increasing pregnancy rates in women with endometrioma
Intervention: Surgery + IVF
Comparison: IVF only

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with IVF only	Risk with Surgery + IVF				
Live birth rate/cycle	351 per 1,000	**288 per 1,000** (226 to 364)	**OR 0.75** (0.54 to 1.06)	356 cases 291 controls (4 observational studies)	⨁⨁◯◯ LOW [a]	Review Nickkho-Amiry 2018
Clinical pregnancy rate/cycle	326 per 1,000	**343 per 1,000** (279 to 412)	**OR 1.08** (0.80 to 1.45)	546 cases 362 controls (7 observational studies)	⨁◯◯◯ VERY LOW [a,b]	Review Nickkho-Amiry 2018
Pregnancy/cycle	371 per 1,000	**342 per 1,000** (261 to 432)	**OR 0.88** (0.60 to 1.29)	412 cases 318 controls (5 observational studies)	⨁◯◯◯ VERY LOW [a,b]	Review Nickkho-Amiry 2018
Oocytes retrieved per cycle	The mean oocytes retrieved per cycle was **6.1 to 10.8** oocytes	MD **0.43 oocytes fewer** (1.67 fewer to 0.8 more)	-	(8 studies)	- [a,b]	Review Nickkho-Amiry 2018
Live birth rate	273 per 1,000	**252 per 1,000** (191 to 324)	**OR 0.90** (0.63 to 1.28)	347 cases 308 controls (5 observational studies)	⨁◯◯◯ VERY LOW [a,b]	Review Hamdan 2015
Clinical pregnancy rate	322 per 1,000	**316 per 1,000** (271 to 363)	**OR 0.97** (0.78 to 1.20)	817 cases 695 controls (11 observational studies)	⨁◯◯◯ VERY LOW [a,b]	Review Hamdan 2015
Number of oocytes retrieved	The mean number of oocytes retrieved was **1.6 to 12.4** oocytes	MD **0.17 oocytes fewer** (0.38 fewer to 0.05 more)	-	1141 (9 studies)	-	Review Hamdan 2015

Explanations
a. Review based on observational data
b. Inconsistency across individual studies

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Hamdan, *et al.*, 2015a)	review and meta-analysis.	5 studies for LBR 11 studies for CPR Endometrioma	surgery versus no treatment		See SOF table	Women with endometrioma who had surgical treatment prior to IVF/ICSI had similar	

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
			No meta-analysis for cystectomy versus aspiration			LBR, CPR, MNOR and MR compared with those women with intact endometrioma. However, these women had a lower AFC and required a higher total gonadotrophin stimulation dose compared with those who had no surgery.	
(Nickkho-Amiry, *et al.*, 2018)	review and meta-analysis.	11 studies Endometrioma	surgery versus no treatment cystectomy versus aspiration		See SOF table	no significant differences in pregnancy rate per cycle, clinical pregnancy rate and live birth rate between womenwho underwent surgery for endometrioma and those who did not.	
(Coccia, *et al.*, 2014)	prospective study	64 infertile women with monolateral endometriomas	IVF/ICSI		Significantly lower numbers of follicles ≥ 16 mm (P = 0.024) and oocytes retrieved (P = 0.001) in the ovaries containing endometrioma In patients with endometriomas ≥ 30 mm, endometrioma size was the most influential contributor to the total number of follicles and oocytes retrieved. (multivariate analysis)	Ovarian endometriomas result in reduced response to ovarian stimulation, compared with the response of the contralateral normal ovary in the same individual. In case of endometriomas <30 mm, basal FSH concentration remains the most important prognostic factor for oocyte retrieval.	
(Şükür, *et al.*, 2020)	retrospective cohort study,	26 women who underwent 44 ART cycles in the presence of ovarian endometrioma Vs a surgery group consisting of 53 women who underwent 58 ART cycles after laparoscopic removal of ovarian endometrioma(s).	ART versus surgery + ART	Cycle cancellation LBR per ET	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%).		

Endometrioma - Aspiration compared to cystectomy

Summary of Findings Table

III.6b Aspiration compared to cystectomy for surgery pre-VF in women with endometrioma

Patient or population: surgery pre-VF in women with endometrioma
Intervention: aspiration
Comparison: cystectomy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with cystectomy	Risk with aspiration				
Pregnancy/cycle	275 per 1,000	**386 per 1,000** (143 to 703)	**OR 1.66** (0.44 to 6.26)	78 cases 131 controls (2 observational studies)	⨁◯◯◯ VERY LOW [a,b]	In Nickkho-Amiry 2018, based on Suganuma 2002 and Takuma 2002
Pregnancy	293 per 1,000	**403 per 1,000** (274 to 545)	**OR 1.63** (0.91 to 2.90)	91 cases 123 controls (3 observational studies)	⨁◯◯◯ VERY LOW [a,b]	In Cohen 2017, based on Lee 2014, Suganuma 2002, Yazbeck 2009

Explanations
a. Review of observational studies
b. Inconsistent results between studies

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Cohen, *et al.*, 2017)	review and meta-analysis	9 studies reporting on fertility and pregnancy	Sclerotherapy vs cystectomy (prior to ART)	number of oocytes retrieved Pregnancy rate	IVF PREGNANCY RATE (asp vs cyst) (3 studies, n=214) OR : 1.63 (0.91-2.90) favouring aspiration Number of oocytes retrieved (asp vs cyst) (3 studies, n=178) OR : 2.71 (0.98-4.44) favouring aspiration Number of oocytes retrieved (asp vs no treatment) (3 studies, n=148) OR : -0.51 (-2.23 – 1.21) favouring no treatment	The number of oocytes retrieved was higher after endometrioma sclerotherapy compared with laparoscopic cystectomy, but clinical pregnancy rates were similar.	See SOF table
(Miquel, *et al.*, 2020)	retrospective study	37 women who underwent ethanol sclerotherapy for endometrioma before ART with those in 37 women undergoing ART only.	Sclerotherapy + ART vs ART	LBR	live birth (OR 2.68; 95%CI 1.13 to 6.36) – increased after Sclerotherapy		

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	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 (Hamdan M, et al., 2015, Nickkho-Amiry et al., 2018) Quality of evidence: ⊕⊕◯◯ When surgical resection of endometrioma prior to ART is necessary, no specific techniques can be recommended
Balance between desirable and undesirable outcomes	Benefits with regards to LBR/pregnancy should be weight against impact on ovarian reserve and possible surgical complications. There are reassuring data with regards to the complication rate associated with surgery for endometriosis (Bafort*, et al.*, 2020a, Byrne*, et al.*, 2018b, Chapron*, et al.*, 1998)
Balance between different outcomes	With no benefit and possible negative effect with regards to ovarian reserve, 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.
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	Surgery is considered acceptable and feasible, although it may require more resources compared to some other treatment options
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.**
GPP	**Surgery for endometrioma prior to ART can be considered to improve endometriosis-associated pain or accessibility of follicles.**

Deep endometriosis

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Bianchi, *et al.*, 2009)	Prospective cohort study	179 infertile patients <38 years with symptoms and/or signs of endometriosis Ten women were lost to follow-up. Patient characteristics in groups A and B, resp, were: age (32±3 vs 32±3 years, ns), infertility duration (29±20 vs 27±17 months, ns), day-3 serum FSH (5.6±2.5 vs 5.9±2.5 IU/L, ns), and previous IVF attempts (1 ± 1 vs 2 ± 1, p = .01).	2 treatment options: IVF without undergoing laparoscopic surgery (group A, n=105) and extensive laparoscopic excision of DE before IVF (group B, n=64).	IVF outcomes	In group B, patients had 5±2 (mean±SD) DIE lesions excised during laparoscopy. The IVF outcomes differed between groups A and B, respectively, with regard to total dose of rFSH for ovulation induction (2380 ± 911 vs 2542 ± 1012 IU, p = .01), number of oocytes retrieved (10 +/- 5 vs 9 ± 5, p = .04), and pregnancy rates (24% vs 41%, p = .004), but not number of embryos transferred (3 ±1 vs 3 ± 1, p = 1). The OR of achieving a pregnancy were 2.45 times greater in group B than in group A.	Extensive laparoscopic excision of DIE significantly improved IVF pregnancy rates of women with infertility-associated DE.	
(Bendifallah, *et al.*, 2017)	Retrospective matched cohort study	110 women	First-line surgery group followed by ART versus exclusive ART with in situ colorectal endometriosis.	pregnancy rates (PRs), live-birth rates (LBRs), and cumulative rates (CRs)	the total LBR and PR were 35.4% (39/110) and 49% (54/110), respectively. The specific cum LBR at the first ICSI-IVF cycle in the first-line surgery group compared with the first-line ART was, respectively, 32.7% vs 13.0%; at the second cycle, 58.9% vs 24.8%; and at the third cycle, 70.6% vs 54.9%. The cumulative LBRs were significantly higher for women who underwent first-line surgery followed by ART compared with first-line ART in the subset of women with good prognosis (age % 35 years and AMH R 2 ng/mL and no adenomyosis) and women with AMH serum level < 2 ng/mL.	First-line surgery may be a good option for women with colorectal endometriosis-associated infertility.	
(Soriano, *et al.*, 2016)	Retrospective cohort study	78 women diagnosed with severe endometriosis during surgery (AFS 3–4) and experienced failed IVF treatments before surgery	laparoscopic surgery for advanced endometriosis	Pregnancy Rates	After surgical treatment 33 women (42.3%) delivered. Three women (9%) conceived spontaneously Women who delivered were younger (32.5 ±4.1 ys vs. 35.5 ±3.8 ys), were less often diagnosed with diminished ovarian reserve before surgery (6% vs. 28.8%), and were more often diagnosed with normal uterine anatomy performing salpingectomy during surgery was associated with a trend of improvement in	Symptomatic women with severe endometriosis and repeated IVF implantation failures may benefit from extensive laparoscopic surgery when performed by an experienced multidisciplinary surgical team to improve IVF outcome.	

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
					delivery rates after surgery (70% in women who delivered vs. 51% in women who failed to deliver).		
(Breteau, *et al.*, 2020)	Retrospective cohort study	104 DE Infertile Patients With at Least 2 Previous IVF/ICSI Failures <43 years Sample = 73 women intending pregnancy	Complete excision	Pregnancy Rates	The postoperative pregnancy rate was 43.8% with a mean time from surgery to pregnancy of 11.1 mo. 21.8% of pregnancies were spontaneous, 31.2% were obtained by IVF, 21.8% by frozen ET, 18.7% by IVF-ICSI, and 3.1% by IUI. Multivariate analysis revealed that ovarian surgery, age ≥35 years old, and stage II endometriosis was associated with the probability of conception.	Infertile women with ≥2 IVF-ICSI failures may be referred for surgery as it appears related to reasonable post-operative PR, particularly when endometriomas surgery is not required/ performed. Surgery for DIE does not routinely delay conception, as it usually occurs during the year following surgery.	

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	From the literature, there is no evidence from randomized controlled trials to recommend performing surgical excision of deep nodular endometriotic lesions prior to ART to improve reproductive outcomes. (Bianchi, et al., 2009, Bendifallah, et al., 2017). Quality of evidence: ⊕◯◯◯
Balance between desirable and undesirable outcomes	Benefits with regards to LBR/pregnancy should be weight against possible surgical complications. There are reassuring data with regards to the complication rate associated with surgery for endometriosis (Bafort*, et al.*, 2020a, Byrne*, et al.*, 2018b, Chapron*, et al.*, 1998). For patients with symptoms, the impact of surgery on these symptoms also need to be considered as a benefit
Balance between different outcomes	With uncertain benefit with regards to LBR/pregnancy, surgery is not recommended. 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.
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	Surgery is considered acceptable and feasible, although it may require more resources compared to some other treatment options
RECOMMENDATION	**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.**

QUESTION III.7 WHAT NON-MEDICAL MANAGEMENT STRATEGIES ARE EFFECTIVE FOR INFERTILITY ASSOCIATED WITH ENDOMETRIOSIS ?

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Zhu, *et al.*, 2014)	RCT	156 infertile women (20-40 y; 12 month of infertility) with minimal/mild endometriosis. After laparoscopic surgery, patients were randomized The follow-up periods were 12 months in Group C and 14 months in complementary medical treatment Group A and B. The pregnant women were further followed up, and labor and pregnancy outcomes were assessed.	Group A (n = 52) oral contraceptive (OC) was administered one pill a day, continuous for 63 days without intervals, Group B (n = 52) OC was administered as group A and then Dan'e mixture was added 30 g/day for the latter 30 days Control group C (n = 52) tried to get pregnant after surgery without compl. treatment. Follow-up periods: 12 months (Group C), 14 months (Group A – B). Pregnant women were further followed up, and labor and pregnancy outcomes were assessed.	Primary outcome: pregnancy rate (PR) and live birth rate (LBR). Secondary outcomes: changes of pelvic pain visual analog scale scores and side effects. Analyses were done as intention-to-treat.	The PR was 46.80% (73/156), and the LBR was 69.86% (51/73). Of the 73 pregnancies, 60 occurred within 12 months of follow-up and 7 of the remaining 13 patients underwent assisted reproductive technology for >1 year. No significant difference was observed in PR and LBR among the three groups. Patients given medical treatment (OCs or OCs plus herbal medicine) had significantly decreased pain scores compared with the laparoscopy alone group.	Combination of laparoscopy with OCs or OCs and herbal medicine does not have more advantages.it is better to conceive immediately after surgery, as there is a 30% chance of conceiving during the 6–12 month period following laparoscopy. who fail to conceive should be treated with superovulation/IUI or IVF according to their preferred choice, the woman's age and other factors. than laparoscopy alone in improving fertility of women with minimal/mild endometriosis.	Sample size calculated to 15% difference in pregnancy rate (N = 52 in each)
(Ding and Lian, 2015)	80 up-to-standard patients random principle.	80 up-to-standard patients (infertile > 12 month) were divided into two different groups exactly according to the random principle.Minimal or mild endometriosis	Chinese herbs vs hormones for 6 month, 1 year FU. Hormone therapy group : 12.5 mg mifepristone orally every day. The therapy started from the first	One year later: transvaginal ultrasonographic changes, serum hormone levels and pregnancy rate were recorded to analysis the effect.	No effect on infertility, same PR	no effect on pregnancy rate, hormonal changes => In conclusion: Chinese herbs effective and safe	randomizatio n, "Up-to standard patients", blinding to the doctors doing the evaluation?, same effect

		confirmed by laparoscopy, age 20-40 Years.	day of their menstrual cycle and lasted for 6 months. The first prescription (folliculae phase) is composed by 20 g (gram) prepared radix rehmanniae, 20 g dodder, 15 g angelica, 15 g salvia, 15 g Caulis Spatholobi, 20 g cyperus rotundus, 12 g curcuma zedoary, 12 g Chuan cattle cane, 15 g poria cocos, 15 g cassia twig, 15 g rhizoma corydalis, 15 g trogopterus dung and 15 g red peony root. The second prescription (lutheal phase) includes 20 g dodder, 20 g herbal epimedii, 10 g cornu cervi degelatinatum, 15 g angelica, 15 g Caulis Spatholobi, 25 g combined spicebush, 15 g poria cocos, 15 g folium artemisiae argyi, 15 g cassia twig, 15 g rhizoma corydalis, 15 g parched white peony root and 10 g liquorice. (6 month)				on pregnancy rate, hormonal changes The conclusion that Chinese herbs are effective and safe is not acceptable based on the study
(Flower, *et al.*, 2012)	Review of RCTS	Two Chinese RCTs involving 158 women (age 23-45 y) were included in this review. Although both these trials described adequate methodology they were of limited quality. Neither trial compared CHM with placebo treatment. (Danazol, Gestrinone).	CHM compared to western medicine (Gestrinone)	Pregnancy rate	There was no significant difference between the CHM and gestrinone groups with regard to the total pregnancy rate (69.6% versus 59.1%; RR 1.18, 95% CI 0.87 to 1.59, one RCT). Two (or3?) years follow-up?	No effect on pregnancy rate (same). Only one study reported fertility rate (Wu 2006)	
(Zhao, *et al.*, 2020)	RCT	202 patients who had laparoscopy for endometriosis-associated infertility with qi stagnation and blood stasis syndrome	randomly divided into the CM treatment group and placebo control group at a ratio of 1:1 using a central block randomization The two groups received continuous intervention at 1-5 days after surgery, for 6 menstrual cycles. Before ovulation, the CM group was treated Huoxue Xiaoyi Granule (); after ovulation, Bushen Zhuyun	primary outcomes: clinical pregnancy rate and pregnancy outcome secondary outcomes: follicular development and endometrial receptivity. Safety evaluations were performed before and after treatment.	CPR and LBR of the CM group were significantly higher than those of the placebo group [44.6% (45/101) vs. 29.7% (30/101), 34.7% (35/101) vs. 20.8% (21/101), both P<0.05]. 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.	Strategies for activating blood circulation-regulating Gan (Liver)-tonifying Shen (Kidney) sequential therapy can effectively improve the clinical pregnancy rate and live birth rate of endometriosis-associated infertility with qi stagnation and blood stasis after laparoscopy, improve follicular development, promote ovulation, improve endometrial receptivity, while being a safe treatment option	It is not mentioned whether the placebo was in 2 different forms according to pre-or post-ovulatory

			Granule (was involved. The control group was treated with placebo.				
(Mier-Cabrera, *et al.*, 2008)	Case controls	34 women with endometriosis received a bar containing vitamins C and E (343 mg and 84 mg, resp) or placebo for 6 months. Plasma and peritoneal fluid levels of malondialdehyde (MDA) and lipid hydroperoxides (LOOHs) were measured for all women and compared between the 2 groups.	6 month treatment/placebo	Pregnancy rate Plasma and peritonela fluide of MDA and LOOH. .	After 4 months, the study group had lower levels of MDA and LOOHs than the control group, and the difference became statistically significant in the 4th month for MDA levels and in the 6th month for LOOH levels. The postintervention PR were 19% and 12% in the supplementation and placebo groups, resp, but the difference was not significant.	Vitamins C and E supplementation was associated with a decrease in the concentration of oxidative stress markers in women with endometriosis. The pregnancy rate, however, did not improve during or after the intervention.	Small study. 6 month intervention.

EVIDENCE TO RECOMMENDATIONS

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.

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.

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.

QUESTION III.8 IS ENDOMETRIOSIS AN INDICATION FOR FERTILITY PRESERVATION (OVARIAN TISSUE / OOCYTES)?

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Cobo, *et al.*, 2020)	Retrospective observational study.	485 women with endometriosis who underwent FP from January 2007 to July 2018. 485 patients with endometriosis out of 1,044 who had their oocytes vitrified returned to use them to attempt pregnancy (return rate 46.5%). Mean age at vitrification was 35.7 ± 3.7 years. 260 patients ≤35y 225 >35y Mean BMI : 22.3 ± 3.7 Stage I–II: 11 (2.3%) Stage III-IV: 474 (97.7%) Surgery for endometrioma: 253 no surgery (52.2%) 151 unilateral surgery 81 bilateral surgery	Vitrification of metaphase II (MII) oocyte	Oocyte survival rate cumulative live-birth rate (CLBR) impact of ovarian surgery	survival rate : 83.2% CLBR : 46.4% impact of ovarian surgery number of vitrified oocytes/cycle: non-surgical: (6.2 ± 5.8) unilateral surgery: (5.0 ± 4.5) bilateral surgery: (4.5 ± 4.4) p<0.05 (nonsurg vs surg) p=ns (uni vs bil) CLBR/patient (%) non-surgical: 124/253 (49.0%) unilateral: 61/151 (40.4%) bilateral: 40/81 (49.3%) Impact on CLBR: Age (adjusted odds ratio [AOR] 0.904; 95% CI, 0.858–0.952), number of oocytes (OR 1.050; 95% CI, 1.025–1.091), survival (A OR 1.011; 95% CI,1.001–1.020) surgery (AOR 1.142; 95% CI 0.778–1.677)	Fertility preservation gives patients with endometriosis a valid treatment option to help them increase their reproductive chances. We suggest performing surgery after ovarian stimulation for FP in young women. In older women, an individualized treatment should be considered.	
{Kim, 2020 #817}	Retrospective study	34 women with endometrioma before a planned ovarian cystectomy mean endometrioma size at diagnosis was 6.0 ± 2.5cm. mean age: 30.7 ± 5.9 yrs serum AMH :1.85 ± 1.14 ng/ml Mean number of oocytes cryopreserved : 4.8 ± 3.2	oocyte cryopreservation for fertility preservation Ovarian stimulation outcomes were compared according to laterality.	clinical usefulness of FP by means of number of oocytes retrieved	number of oocytes cryopreserved in bilateral endometrioma compared with unilateral endometrioma patients was 4.1 ± 2.9 versus 5.7 ± 3.4 (P = 0.600). In the propensity score-matched cohort (n = 22 per group), the number of oocytes retrieved was significantly lower in the patients with endometrioma undergoing FP compared with that in patients without endometrioma (5.4 ± 3.8 versus 8.1 ± 4.8; P = 0.045).		

					A total of 13 (38.2%) patients with endometrioma underwent repeated stimulation. The median (IQR) number of cryopreserved oocytes at the first and the second cycle were 3.0 (2.5-6.0) and 5.0 (2.5-7.5), resp.		

INCLUDED AS BACKGROUND INFORMATION
(Donnez*, et al.*, 2018, ESHRE Guideline Group on Female Fertility Preservation*, et al.*, 2020, Somigliana and Vercellini, 2020)

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	The study of Cobo 2020 reports on 1,044 women who were diagnosed with endometriosis and who decided to bank their oocytes, and more specifically on the 485 women (43%) that returned and used the oocytes for attempting pregnancy. The study reports a high rate of success (CLBR : 46.4%), but does not compare to women undergoing IVF with fresh cycles. The evidence for benefit of FP is based on a single, retrospective study, and hence assessed as very low quality. Quality of evidence: ⊕◯◯◯
Balance between desirable and undesirable outcomes	The benefit with regards to the chances of a live birth would need to be weighted against the risks associated with oocyte cryopreservation
Balance between different outcomes	If a woman will ultimately need in vitro fertilization procedures, it would be better to store eggs at a younger age, in these women the benefits of oocyte cryopreservation would outweigh the risks (which are the same as for IVF). For these women with endometriosis, fertility preservation may increase their future chances of pregnancy, but there is no evidence on criteria to select those women. For the general endometriosis population, the benefit is limited and the clinical risks associated with oocyte cryopreservation do not outweigh this possible benefit. Based on these considerations, the GDG formulated a strong recommendation for counselling and information provision.
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	Oocyte cryopreservation is expensive. Advocating for systematic fertility preservation in all women with endometriosis can cause wastage of resources. Cobo et al has demonstrated feasility of oocyte cryopreservation
RECOMMENDATION	**There is currently no evidence to support fertility preservation for all women with endometriosis. Similarly, there is no evidence to select those endometriosis patients that may benefit from fertility preservation. Based on these considerations, the GDG formulated a recommendation for counselling and information provision.** **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.**

QUESTION III.9 WHAT IS THE IMPACT OF ENDOMETRIOSIS ON PREGNANCY AND OBSTETRIC OUTCOMES?

This question was considered a narrative questions, as it did not investigate the impact of a certain intervention on a set of predefined outcomes. The section is largely based on recent systematic reviews summarizing the evidence on the topic. While no recommendations could be given recommending actions, it was found relevant to add recommendations to increase knowledge on the subject, and recommendations on safety aspects, related to knowledge of complications, monitoring and detection.

Effect of pregnancy on endometriotic lesions

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Intervention	Outcome measures	Effect size	Authors conclusion	Comments
(Leeners, *et al.*, 2018)	Systematic review	Endometriosis 5 small observational studies + 6 case reports 22 case reports/small case series 6 studies on histology 8 studies on the role of pregnancy	Pregnancy	development of endometriotic lesions / endometrioma during and after pregnancy histology of endometriotic lesions in pregnancy role of pregnancy in development/ recurrence of endometriosis		Available data on the development of endometriosis during and after pregnancy show fewer beneficial effects than previously reported. Therefore, women aiming for pregnancy on the background of endometriosis should not be told that pregnancy may be a strategy for managing symptoms and reducing progression of the disease.	
(Leone Roberti Maggiore, *et al.*, 2016)	Systematic / narrative review	endometriosis	pregnancy	Suspicion of malignant degeneration of decidualized endometriosis: imaging pattern and treatment issues Complications of a pre-existing endometriosis during pregnancy Endometriosis and pregnancy outcomes		Complications of endometriosis during pregnancy are rare and there is no evidence that the disease has a major detrimental effect on pregnancy outcome. Therefore, pregnant women with endometriosis can be reassured on the course of their pregnancies although the physicians should be aware of the potential increased risk of placenta previa. Current evidence does not support any modification of conventional monitoring of pregnancy in patients with endometriosis.	

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	The evidence (summarized in a high quality systematic review), shows a variable impact of pregnancy on endometriotic lesions. The review is based on a low number of small observational studies, few case reports and some other studies providing indirect support to the conclusion. Quality of evidence: ⊕◯◯◯ (limited number of observational data)
Balance between desirable and undesirable outcomes	Benefits of pregnancy with regards to disease progression, versus the risks with regards to disease progression.

Balance between different outcomes	Patients are being advised to become pregnant to cure their endometriosis, and the data indicate that this advise is incorrect. The GDG therefore considered it relevant and important to formulate a recommendation that women with endometriosis should be informed and that they should not be advised to become pregnant with the sole purpose of treating endometriosis.
Patient values and preference	
Resource use, equity, acceptability and feasibility	It used to be advised for women to attempt pregnancy for curing endometriosis.
RECOMMENDATION	**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.**

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	Data show that endometrioma may change appearance during pregnancy, but that this is often unknown and not recognized. Data are derived from a review based on limited observational data. Quality of evidence: ⊕◯◯◯
Balance between desirable and undesirable outcomes	Correct actions to follow-up an endometrioma changing during pregnancy versus overtreatment (surgery, pregnancy termination) linked to incorrect assessment.
Balance between different outcomes	A change in appearance of an endometrioma during pregnancy may lead to surgical intervention and termination of pregnancy, while possibly harmless. Referral to a centre with expertise for diagnosis and if needed treatment, may prevent overtreatment and harm.
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	Actions from incorrect assessment may create overtreatment (surgery, pregnancy termination) with significant resource use.
RECOMMENDATION	**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.**

Possible complications during pregnancy from a pre-existing endometriosis lesion

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments

(Leone Roberti Maggiore*, et al.*, 2016)	Systematic / narrative review	endometriosis	pregnancy	Suspicion of malignant degeneration of decidualized endometriosis: imaging pattern and treatment issues Complications of a pre-existing endometriosis during pregnancy Endometriosis and pregnancy outcomes		Complications of endometriosis during pregnancy are rare and there is no evidence that the disease has a major detrimental effect on pregnancy outcome. Therefore, pregnant women with endometriosis can be reassured on the course of their pregnancies although the physicians should be aware of the potential increased risk of placenta previa. Current evidence does not support any modification of conventional monitoring of pregnancy in patients with endometriosis.	
(Leone Roberti Maggiore*, et al.*, 2017)	Systematic review	women with endometriosis, particularly deep endometriosis	pregnancy	Obstetrical complications		The strongest evidence shows that DE is associated with higher rates of placenta previa; for other obstetrical outcomes, such as miscarriage, intrauterine growth restriction, preterm birth and hypertensive disorders, results are controversial. Although it is unlikely that surgery of DE may modify the impact of the disease on the course of pregnancy, no study has yet investigated this issue.	
(Glavind*, et al.*, 2018)	Systematic review	women with endometriosis	pregnancy	Obstetrical outcome including spontaneous hemoperitoneum and bowel perforation		Overall, the results showed an increased risk of preterm delivery, antepartum haemorrhage, delivery by caesarean section, and the rare complications of spontaneous haemorrhage in pregnancy and spontaneous bowel perforation. There is no firm evidence for any increased risk of preeclampsia, having a child born small for gestational age, stillbirth, or postpartum haemorrhage. In conclusion, pregnant patients with endometriosis should be offered special clinical attention.	
(Lier*, et al.*, 2017)	systematic review	women with endometriosis	pregnancy	Spontaneous hemoperitoneum in pregnancy (SHiP)		In conclusion, SHiP is a very serious complication of pregnancy, highly associated with adverse pregnancy outcomes and particularly relevant to women with endometriosis. Currently preventive measures are lacking, therefore increasing the awareness and recognition of SHiP is crucial to improve pregnancy outcomes.	

CASE REPORTS
(Berlac*, et al.*, 2017, Chester and Israfil-Bayli, 2015, Chiodo*, et al.*, 2008, Fettback*, et al.*, 2015, Leone Roberti Maggiore*, et al.*, 2015)

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.

Impact of endometriosis on pregnancy and neonatal outcomes

Summary of Findings Table III.9

			Risk in women without endometriosis	Risk in women with endometriosis	Odds ratio		
1ST trimester	Miscarriage	↑ ?			NC/ART	No meta-analysis performed	(Leone Roberti Maggiore, *et al.*, 2016)
			19% 60/313	15% 48/313	ART	0.76 (95% CI 0.50-1.16)	(Leonardi, *et al.*, 2016)
			29% 139/478	19% 187/964	NC/ART	adjusted IRR 1.70 (95% CI 1.34-2.16)	(Santulli, *et al.*, 2016)
			5.4% 450/8280	12.3% 662/5375	NC/ART	OR 1.76 (95% CI 1.44-2.15)	(Saraswat, *et al.*, 2017)
			10.7% 26219/243100	10.3% 4192/40808	NC/ART	OR 1.30 (95% CI 1.25–1.35)	(Horton, *et al.*, 2019)
	Ectopic pregnancy	↑	1.59% 7055/441649[1]	2.0% 1230/61589[1]	NC/ART	OR 2.66 (95% CI 1.14–6.21)[1]	(Yong, *et al.*, 2020)
			2.1% 2278/106948[2]	3.9% 1162/30042[2]		OR 2.16 (95% CI 1.67–2.79)[2]	
2nd and 3Rd trimester	Gestational diabetes	↑	nd	nd	NC/ART	OR 1.26 (95% CI 1.03-1.55)	(Lalani, *et al.*, 2018).
	Premature rupture of membranes	↑	nd	nd	NC/ART	OR 2.33 (95% CI 1.39-3.90)	(Lalani, *et al.*, 2018).
	Preterm birth	↑	4.15% 125359/3019058	6.6% 2868/43267	NC/ART	OR 1.70 (95% CI 1.40-2.06)	(Lalani, *et al.*, 2018).
			5.2% 83914/1609742	6.3% 1588/25283	NC/ART	OR 1.38 (95% CI 1.01-1.89)	(Horton, *et al.*, 2019)
			5.2% 74134/1435075	7.0% 767/10994	NC	OR 1.59 (95% CI 1.32-1.90)	(Perez-Lopez, *et al.*, 2018)
			7.0% 3339/47842	10.3% 288/2804	ART	OR 1.43 (95% CI 1.14-1.79)	(Perez-Lopez, *et al.*, 2018)
	Placenta praevia	↑	0.66% 7862/1178425	2.36% 648/27395	NC/ART	OR 3.31 (95% CI 2.37-4.63)	(Lalani, *et al.*, 2018).
			0.52% 6299/1206556	2.15% 560/26023	NC/ART	OR 3.09 (95% CI 2.04-4.68)	(Horton, *et al.*, 2019)
	Hypertensive disorders and pre-eclampsia	↑	nd	nd	NC/ART	OR 1.21 (95% CI 1.05-1.39)	(Lalani, *et al.*, 2018).
	Pre-eclampsia	↑	nd	nd	NC/ART	OR 1.18 (95% CI 1.01-1.39)	(Lalani, *et al.*, 2018).
			2.6% 75750/2890958	3.2% 1250/39231	NC/ART	OR 1.18 (95% CI 1.03-1.36)	(Horton, *et al.*, 2019)
	Stillbirth	↑	0.39% 9971/2547756	0.53% 202/38009		OR 1.29 (95% CI 1.10-1.52)	(Lalani, *et al.*, 2018).
			0.38% 10114/2613290	0.51% 179/35065	NC/ART	OR 1.25 (95% CI 1.08-1.45)	(Horton, *et al.*, 2019)
	Caesarean section	↑	12.6%	25.0%	NC/ART	OR 1.86 (95% CI 1.51-2.29)	(Lalani, *et al.*, 2018).

			370803/2952659	10511/41974			
			14.3% 234936/1642096	24.6% 5063/20537	NC/ART	OR 1.98 (95% CI 1.64-2.38)	(Horton, *et al.*, 2019)
Neonatal outcomes	Ante-partum hemorrhage	↑	nd	nd	NC/ART	OR 1.69 (95% CI 1.38-2.07)	(Lalani, *et al.*, 2018).
	Placental abruption	↑ ?	nd	nd	NC/ART	OR 1.46 (95% CI 0.98-2.19)	(Lalani, *et al.*, 2018).
			0.61% 7205/1166990	1.10% 273/24658	NC/ART	OR 1.87 (95% CI 1.65-2.13)	(Horton, *et al.*, 2019)
	Post-partum bleeding	↔	nd	nd	NC/ART	OR 1.19 (95% CI 0.89-1.59)	(Lalani, *et al.*, 2018).
	Small for gestational age	↑	nd	nd	NC/ART	OR 1.28 (95% CI 1.11-1.49)	(Lalani, *et al.*, 2018).
			2.5% 37981/1521982	2.8% 406/14509	NC/ART	OR 1.16 (95% CI 1.05-1.28)	(Perez-Lopez, *et al.*, 2018)
	Admission to NICU	↑	nd	nd	NC/ART	OR 1.39 (95% CI1.08-1.78)	(Lalani, *et al.*, 2018).
			12.1% 17165/141471	14.6% 147/1009	NC/ART	OR 1.29 (95% CI 1.07-1.55)	(Horton, *et al.*, 2019)
	Neonatal death	↑	nd	nd	NC/ART	OR 1.78 (95% CI 1.46-2.16)	(Lalani, *et al.*, 2018).

[1] Case control studies
[2] cohort studies

EVIDENCE TABLE

Reference	Study Type	Patients	Intervention	Outcome measures	Effect size	Authors conclusion	Comments
Early pregnancy (1st trimester)							
(Leone Roberti Maggiore, *et al.*, 2016)	Systematic / narrative review	endometriosis	pregnancy	Suspicion of malignant degeneration of decidualized endometriosis: imaging pattern and treatment issues Complications of a pre-existing endometriosis during pregnancy Endometriosis and pregnancy outcomes	See SOF table III.9	Complications of endometriosis during pregnancy are rare and there is no evidence that the disease has a major detrimental effect on pregnancy outcome. Therefore, pregnant women with endometriosis can be reassured on the course of their pregnancies although the physicians should be aware of the potential increased risk of placenta previa. Current evidence does not support any modification of conventional monitoring of pregnancy in patients with endometriosis.	
(Santulli, *et al.*, 2016)	retrospective cohort study	284 Endometriosis vs 466 control	pregnancy	Previous history of miscarriage	See SOF table III.9	Endometriosis-affected women display a significantly higher rate of previous spontaneous miscarriages than endometriosis-free controls.	
[Kohl Schwartz, 2017 #567]	retrospective observational study	940 women, 505 with endometriosis + 435 matched disease-free controls	na	Miscarriage rate		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%). Subgroup subfertile women : Significant difference (50.0% [40.7%–59.4%]) vs. (25.8%; 95%CI 8.5% to 41.2%) Subgroup fertile women: no difference (24.5%; 95%CI 16.3% to 31.6% vs. 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%)	
(Saraswat, *et al.*, 2017)	national population based cohort study	5375 women with surgically confirmed endometriosis vs 8710 women without endometriosis	pregnancy	Miscarriage Ectopic pregnancy stillbirths and other pregnancy complications such as hypertensive disorders of pregnancy, antepartum and postpartum haemorrhage, operative delivery and preterm births.	See SOF table III.9	Endometriosis predisposes women to an increased risk of early pregnancy loss and later pregnancy complications.	
(Yong, *et al.*, 2020)	Systematic review	endometriosis	pregnancy	Ectopic pregnancy	See SOF table III.9	Possible evidence of an association between endometriosis and ectopic pregnancy was observed (OR= 2.16–2.66). However, these results should be considered with caution, owing to high heterogeneity among studies. Continued research is needed to delineate the pregnancy implications of endometriosis.	
Second and third trimester pregnancy + neonatal outcomes							
(Leone Roberti Maggiore, *et al.*, 2016)	Systematic / narrative review	endometriosis	pregnancy	Suspicion of malignant degeneration of decidualized endometriosis: imaging pattern and treatment issues Complications of a pre-existing endometriosis during pregnancy Endometriosis and pregnancy outcomes	See SOF table III.9	Complications of endometriosis during pregnancy are rare and there is no evidence that the disease has a major detrimental effect on pregnancy outcome. Therefore, pregnant women with endometriosis can be reassured on the course of their pregnancies although the physicians should be aware of the potential increased risk of placenta previa. Current evidence does not support any modification of conventional monitoring of pregnancy in patients with endometriosis.	
(Lalani, *et al.*, 2018)	Systematic review	endometriosis	pregnancy	maternal, fetal and neonatal outcomes	See SOF table III.9	Women with endometriosis are at elevated risk for serious and important adverse maternal (pre-eclampsia, gestational diabetes, placenta praevia and Caesarean section) and fetal or neonatal outcomes (preterm birth, PPROM, small for gestational age, stillbirth and neonatal death).	
(Perez-Lopez, *et al.*, 2018)	Systematic review	endometriosis	Pregnancy (spontaneous/ART)	Preterm Birth	See SOF table III.9	Endometriosis is associated with increased PB risk in both SC and women who obtained pregnancy using ART. Prospective studies evaluating relevant outcomes are needed to confirm these results.	
(Horton, *et al.*, 2019)	Systematic review	endometriosis	pregnancy	Reproductive, obstetric, and perinatal outcomes	See SOF table III.9	The complications are possibly caused by dysfunctional uterine changes leading to implantation and placentation issues and therefore could potentially have far-reaching consequences as suggested by Barker's hypothesis. Our findings would suggest that women with these conditions should ideally receive pre-natal counselling and should be considered higher risk in pregnancy and at delivery, until evidence to the contrary is available. In order to expand our knowledge of these conditions and better advise on future management of these patients in reproductive and maternal medicine, a more unified approach to studying fertility and reproductive outcomes with longer term follow-up of the offspring and attention to the subtype of disease is necessary.	

EVIDENCE TO RECOMMENDATIONS - Early pregnancy (1st trimester)

The evidence (and its quality)	Both miscarriage rate and ectopic pregnancy rate are increased in women with endometriosis versus controls, although this is based on low/moderate quality data. Quality of evidence: ⊕⊕◯◯
Balance between desirable and undesirable outcomes	Not applicable
Balance between different outcomes	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. As there is no data on prevention of miscarriage or ectopic pregnancy, awareness is recommended
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	Not applicable (recommendation for increased awareness)
RECOMMENDATION	**Clinicians should be aware that there may be an increased risk of first trimester miscarriage and ectopic pregnancy in women with endometriosis.**

EVIDENCE TO RECOMMENDATIONS - Second and third trimester pregnancy + neonatal outcomes

The evidence (and its quality)	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. Quality of evidence: ⊕⊕◯◯
Balance between desirable and undesirable outcomes	Not applicable
Balance between different outcomes	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.
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	Not applicable (recommendation for increased awareness)
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.**

QUESTION IV.1 IS THERE A ROLE FOR SECONDARY PREVENTION OF RECURRENCE OF DISEASE AND PAINFUL SYMPTOMS IN PATIENTS TREATED FOR ENDOMETRIOSIS?

Surgical technique for prevention of recurrence: Excisional surgery compared to Ablative surgery

Summary of Findings Table

IV.1a Excisional surgery compared to ablative surgery for secondary prevention in ovarian endometriomata

Patient or population: secondary prevention in ovarian endometriomata
Intervention: Excisional surgery
Comparison: Ablative surgery

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Ablative surgery	Risk with Excisional surgery				
Recurrence of dysmenorrhea	77 per 100	**33 per 100** (16 to 55)	**OR 0.15** (0.06 to 0.38)	104 (2 RCTs)	⊕⊕◯◯ LOW [a,b]	
Recurrence of dyspareunia	75 per 100	**19 per 100** (3 to 60)	**OR 0.08** (0.01 to 0.51)	27 (1 RCT)	⊕◯◯◯ VERY LOW [c]	
Recurrence of non-menstrual pelvic pain	53 per 100	**10 per 100** (2 to 39)	**OR 0.10** (0.02 to 0.56)	37 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	
Recurrence of endometrioma	26 per 100	**13 per 100** (6 to 25)	**OR 0.41** (0.18 to 0.93)	164 (2 RCTs)	⊕⊕◯◯ LOW [a,b]	
Requirement of further surgery	23 per 100	**6 per 100** (1 to 19)	**OR 0.21** (0.05 to 0.79)	100 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	

Explanations
a. Evidence based on two small trials
b. In all studies the women, operators and examining doctors at the time of follow up were aware of the operative procedure performed, which may adversely affect the reporting of results.
c. Evidence based on a single trial

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Hart*, et al.*, 2008, Hart*, et al.*, 2005)	**Review**	3 RCTs evaluating the most effective surgical technique for treating ovarian endometrioma,	1. Excision of cyst capsule (stripping) vs 2. Drainage and electrocoagulation of	**Primary endpoints** - Relief of pain (as measured by VAS or dichotomous data)	**Primary endpoints** - Both techniques treated pain 100% effectively after short-term follow up. - LPS excision associated with significant benefit on the recurrence of **dysmenorrhea (OR 0.15,**	Excisional surgery for endometrioma is associated with a reduced recurrence of dysmenorrhea, dyspareunia, non-menstrual	

		including 229 patients	the cyst wall (ablation) Both LPS and LPT approaches included	- Pregnancy rate, both biochemical and clinical, (either spontaneous or with ARTs) **Secondary outcomes** - Recurrence of endometrioma - Conversion from planned LPS to LPT - Ovarian function (changes in FSH or onset of menopausal symptoms) QoL (patients' satisfaction or objective scales)	**95% CI 0.06 to 0.38), dyspareunia (OR 0.08, 95% CI 0.01 to 0.51) and noncyclic pelvic pain (OR 0.10, 95% CI 0.02 to 0.56)** - Chance of spontaneous pregnancy at 12 months significantly favored LPS excision technique **(OR 5.24, 95%CI 1.92 to14.27)** - **Overall spontaneous conception rate** favored LPS excision **(OR 5.21, 95% CI 2.04 to13.29)** - Non conclusive evidence to favor one technique over the other with respect to pregnancy outcome after controlled ovarian stimulation and IUI **(1.40, 95% CI 0.47 to 4.15)** **Secondary outcomes** - **Recurrence of endometrioma** significantly reduced for LPS excision (**OR 0.41, 95% CI 0.18 to 0.93)** - **Conversion from LPS to LPT**: both techniques have low chance of LPT conversion (no power to detect a difference) - **Ovarian function**. Statistically significant difference in terms of number of follicles that developed after ovarian stimulation in favor of excision **(MD 0.6, 95% CI 0.04 to 1.16)** **Reoperation rate**. Significantly reduced requirement for further surgery in women undergoing excision **(OR 0.21, 95% CI 0.05 to 0.79)**	pelvic pain and also with a reduced endometrioma recurrence rate. Also, greater conception rates in women treated with excisional surgery. More favorable response to ovarian stimulation after excisional surgery. Additionally, reduced requirement for further surgery after endometrioma excision.	

INCLUDED AS BACKGROUND INFORMATION
(Ceccaroni*, et al.*, 2019),(International working group of AAGL ASRM ESGE ESHRE and WES*, et al.*, 2021)

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	Evidence suggests that Cystectomy is probably superior to drainage and coagulation in women with ovarian endometrioma (≥ 3cm) with regard to the recurrence of endometriosis-associated pain and the recurrence of endometrioma. Quality of evidence: ⊕⊕◯◯ (based on the evidence level for the most important outcomes, recurrence of dysmenorrhea and endometrioma)
Balance between desirable and undesirable outcomes	Benefits: reduction of endometrioma recurrence and endometriosis related symptoms Risk: risk related to surgical technique
Balance between different outcomes	Ovarian cystectomy seems to have better outcomes for endometrioma and symptoms recurrence compared to drainage and electrocoagulation
Patient values and preference	Unclear. Patients may benefit of counselling about different options in case of surgery
Resource use, equity, acceptability and feasibility	No clear relevance of resource use, acceptability and feasibility with regards to the surgical technique used.

RECOMMENDATION	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.

Postsurgical medical therapy for secondary prevention

Summary of Findings Table

IV.1b Postsurgical medical therapy compared to placebo or no medical therapy for secondary prevention

Patient or population: secondary prevention
Intervention: postsurgical medical therapy
Comparison: placebo or no medical therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no medical therapy	Risk with postsurgical medical therapy				
Pain recurrence follow up: 13-24 months	286 per 1,000	**200 per 1,000** (134 to 294)	**RR 0.70** (0.47 to 1.03)	312 (3 RCTs)	⨁⨁◯◯ LOW [a,b]	(based on Busacca 2001, Muzii 2000, and Vercellini 1999)
Disease recurrence follow up: 13-24 months	249 per 1,000	**99 per 1,000** (67 to 144)	**RR 0.40** (0.27 to 0.58)	571 (4 RCTs)	⨁⨁◯◯ LOW [a,b]	(based on Cucinella 2013, Seracchioli 2010, Sesti 2009, and Tsai 2004)
Disease recurrence (radiologic/clinical) follow up: ≥12 months	264 per 1,000	**121 per 1,000** (98 to 148)	**RR 0.46** (0.37 to 0.56)	1766 (14 RCTs)	⨁⨁◯◯ LOW [c,d]	based on Zakhari 2020
Change in pain scores follow up: ≥12 months	-	SMD **0.37 SD lower** (0.53 lower to 0.21 lower)	-	652 (7 RCTs)	⨁⨁◯◯ LOW [c,d]	based on Zakhari 2020

Explanations
a. Downgraded for the quality of the included studies
b. Imprecision detected
c. RCTs and observational studies combined
d. Direction of the effect is not consistent across studies

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Chen, *et al.*, 2020)	Cochrane review	Endometriosis	postsurgical medical therapy versus placebo or no medical therapy	Pain / Pain recurrence Disease recurrence Follow up > 12 months	See SOF table IV.1b	- uncertain about the effect of postsurgical medical therapy on pain recurrence	

						- There may be a reduction of disease recurrence in favour of postsurgical hormonal therapy, (RR 0.40, 95% CI 0.27 to 0.58; I2 = 57%; 4 RCTs, n = 571; low-quality evidence	
(Zakhari, *et al.*, 2020a)	systematic review and meta-analysis	Endometriosis 17 studies (13 RCTs and 4 cohort studies), with 2137 patients (1189 receiving treatment and 948 controls)	post-operative hormonal suppression	post-operative endometriosis recurrence (determined by imaging or recurrence of symptoms, at least 12 months post-operatively) change in endometriosis-related pain.	See SOF table IV.1b Subanalysis Progestin: RR 0.17 (0.02;1.36) (1RCT; n= 32)	Hormonal suppression should be considered for patients not seeking pregnancy immediately after endometriosis surgery in order to reduce disease recurrence and pain. Various hormonal agents have been shown to be effective, and the exact treatment choice should be individualised according to each woman's needs.	

INCLUDED AS BACKGROUND INFORMATION
Furness 2004

Postsurgical medical therapy for secondary prevention

Summary of Findings Table

IV.1c Postsurgical OCP / LNG-IUS compared to placebo or no medical therapy for secondary prevention after endometriosis surgery

Patient or population: secondary prevention after endometriosis surgery
Intervention: Postsurgical OCP / LNG-IUS / Progestagens
Comparison: placebo or no medical therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no medical therapy	Risk with Postsurgical OCP				
Disease recurrence (radiologic/clinical) follow up: ≥12 months	269 per 1,000	**86 per 1,000** (62 to 118)	**RR 0.32** (0.23 to 0.44)	854 (6 RCTs)	⨁⨁◯◯ LOW [a,b]	(sub-analysis in Zakhari 2020)
Outcomes	**Risk with placebo or no medical therapy**	**Risk with Postsurgical LNG-IUS**	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Dysmenorrhea recurrence follow up: ≥12 months	388 per 1,000	**116 per 1,000** (62 to 221)	**RR 0.30** (0.16 to 0.57)	171 (3 RCTs)	⨁⨁◯◯ LOW [a,c]	(Song 2018)
Endometrioma recurrence follow up: ≥12 months	258 per 1,000	**155 per 1,000** (80 to 294)	**RR 0.60** (0.31 to 1.14)	134 (2 RCTs)	⨁◯◯◯ VERY LOW [a,c,d]	(Song 2018)

Explanations
a. RCTs and observational studies combined
b. Direction of the effect is not consistent across studies
c. Small studies and small number of included patients
d. Large confidence intervals, suggestive of imprecision

IV.Id Postsurgical GnRHa compared to placebo or no medical therapy for secondary prevention after endometriosis surgery

Patient or population: secondary prevention after endometriosis surgery
Intervention: Postsurgical GnRHa
Comparison: placebo or no medical therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no medical therapy	Risk with GnRH agonist for postsurgical medical therapy				
Disease recurrence (radiologic/clinical) follow up: ≥12 months	227 per 1,000	**150 per 1,000** (116 to 197)	**RR 0.66** (0.51 to 0.87)	929 (7 RCTs)	⊕⊕◯◯ LOW [a,b]	(sub-analysis in Zakhari 2020)
Endometriosis recurrence	286 per 1,000	**440 per 1,000** (356 to 503)	**OR 1.96** (2.53 to 1.38)	1184 (6 observational studies)	⊕⊕◯◯ LOW	Zakhari 2020b (Dienogest)

Explanations
a. RCTs and observational studies combined
b. Direction of the effect is not consistent across studies

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
OCP							
(Zakhari, *et al.*, 2020a)	systematic review and meta-analysis	Endometriosis 17 studies (13 RCTs and 4 cohort studies), with 2137 patients (1189 receiving treatment and 948 controls)	post-operative hormonal suppression	post-operative endometriosis recurrence (determined by imaging or recurrence of symptoms, at least 12 months post-operatively) change in endometriosis-related pain.	Subanalysis for OCP See SOF table IV.1c Sub-analysis LNG-IUS RR 0.21 (0.08;0.56) (2RCTs; n=90)	Hormonal suppression should be considered for patients not seeking pregnancy immediately after endometriosis surgery in order to reduce disease recurrence and pain. Various hormonal agents have been shown to be effective, and the exact	

						treatment choice should be individualised according to each woman's needs.	
(Seracchioli, *et al.*, 2009)	SR (RCT and Non RCT)	Endometriosis	evaluate the effect of post-operative use of OCP in preventing symptom recurrence, and/or anatomical relapse of endometriosis	Seven studies that evaluated the effects of post-operative OCP on prevention of endometriosis recurrence were considered for this review.	A reduction in anatomical relapse rate was observed when oral contraceptive therapy was administered for more than 1 year after conservative surgery. Post-operative use of OCP was associated with a reduction in frequency and intensity of dysmenorrhoea recurrence. No association was found between OCP therapy and dyspareunia prevention, although the effect of OCP on chronic pelvic pain was conflicting	Long-term OCP therapy can be a reliable adjuvant post-operative measure to prevent or reduce frequency/severity of recurrent dysmenorrhoea and anatomical relapse of endometriosis. Since both continuous and cyclic OCP administration regimens seem to have comparable effects, the choice of regimen can be modulated according to patient preferences. The protective effect seems to be related to the duration of treatment.	No meta-analysis, overlap in selected studies with Zakhari 2020
Progestagens : LNG-IUS							
(Abou-Setta, *et al.*, 2013)	Review	3 RCT included Two RCTs (95 patients): 1. LNG-IUD vs expectant management One RCT (40 patients): LNG-IUD vs GnRH agonists	RCTs published until June 2012 comparing: - LNG-IUD insertion within 3 months of surgery - No post-operative treatment - Placebo (inert IUD) Other treatments	- Pain recurrence - Patients' satisfaction - Number of patients not completing the allocated treatment	2 RCT (95 patients) LNG-IUD vs no treatment - Statistically significant reduction in the recurrence of dysmenorrhea (RR 0.22, 95% CI 0.08 to 0.60) - Higher patients' satisfaction with LNG-IUD, not statistically significant (RR 1.21, 95% CI 0.80 to 1.82) - Higher number of women reporting a change in menstruation with LNG-IUD (RR 37.80, 95% CI 5.40 to 264.60) - Comparable number of women who did not complete the allocated treatment (RR 0.66, 95% CI 0.08 to 5.25) 1 RCT (40 patients) LNG-IUD vs GnRH agonists Lower pain scores in women with LNG-IUD compared to those receiving GnRH agonists, but with no statistical significance (MD -0.16, 95% CI -2.02 to 1.70)	Limited but consistent evidence showing that postoperative insertion of LNG-IUD reduces the recurrence of painful periods.	
(Zakhari, *et al.*, 2020a)	systematic review and meta-analysis	Endometriosis	post-operative hormonal suppression	post-operative endometriosis recurrence change in endometriosis-related pain.	Sub-analysis LNG-IUS RR 0.21 (0.08;0.56) (2RCTs; n=90)		

(Song, *et al.*, 2018)	meta-analysis	7 studies were selected: 7 studies included 4 randomized controlled trials with 212 patients, 1 prospective cohort study with 88 patients, and 2 retrospective studies with 191 patients.	levonorgestrel releasing intrauterine system (LNG-IUS) versus other treatments as a postoperative maintenance therapy for endometriosis	pain reduction, recurrence prevention, side effects and patients' satisfaction.	See SOF table IV.1c Meta-analysis showed that LNG-IUS was significantly effective in reducing pain after surgery (MD = 12.97, 95% CI: 5.55–20.39), with a comparable effect to GnRHa (MD = 0.16, 95% CI:2.02 to 1.70). LNG-IUS was also effective in decreasing the recurrence rate (RR = 0.40, 95% CI: 0.26–0.64), with an effect comparable to OCP (OR = 1.00, 95% CI: 0.25–4.02) and danazol (RR = 0.30, 95% CI: 0.03–2.81). Furthermore, patients' satisfaction with LNG-IUS was significantly higher than that with OCP (OR = 8.60, 95% CI: 1.03–71.86). Vaginal bleeding was significantly higher in the LNG-IUS group than in the GnRHa group (RR = 27.0, 95% CI: 1.71–425.36).	Our meta-analysis found a positive effect of LNG-IUS as a postoperative maintenance therapy for endometriosis on pain relief, prevention of dysmenorrhea recurrence, and patients' satisfaction.	
(Lee, *et al.*, 2018)	retrospective	285 patients – endometriosis after laparoscopic surgery	Patients were grouped into no treatment (n = 83), treatment with dienogest (n =130) and treatment with LNG-IUS (n =72) after surgery	pain scores rates of disease recurrence treatment discontinuation rate 6, 12 and 24 months after the surgery	LNG-IUS vs no treatment Recurrence: 7 (9.7) versus 26.5 (32.5) LNG-IUS versus dienogest (not considered: the LNG-IUS group is older, it is difficult to compare the efficacy between dienogest and LNG-IUS in present study)	LNG-IUS treatment in the patients with endometriosis is effective for post-operative pain control and preventing recurrence,	
Progestagens : dydrogesterone							
(Trivedi, *et al.*, 2007)	open, prospective, multicenter study	90 patients suffering from minimal, mild, moderate or severe endometriosis, with or without infertility, who had undergone laparoscopy,	dydrogesterone 10 mg/day (or 20 mg/day in severe cases) orally from day 5 to day 25 of each cycle for 3–6 months	Efficacy and safety	Pelvic pain, dysmenorrhea and dyspareunia improved significantly ($p<0.05$) after the first cycle of treatment. By the end of the 6th cycle, the reduction in pelvic pain, dysmenorrhea and dyspareunia was 95%, 87% and 85%, respectively. The amount of menstrual bleeding fell significantly ($p<0.05$) after 2 months (712%) and this significant reduction was maintained until the end of the study. The duration of bleeding	Overall, dydrogesterone therapy was rated as excellent to good by 74% of patients and 70% of physicians. No adverse events were reported. In conclusion, dydrogesterone is an effective and safe post-laparoscopic treatment for endometriosis.	

					was also reduced significantly (p<0.05) throughout the study, starting after the first month of treatment (710%). A total of 21.1% of the patients were considered cured and 66.7% showed improvement.		
GnRH agonist							
(Zakhari, *et al.*, 2020a)	systematic review and meta-analysis	Endometriosis	post-operative hormonal suppression	post-operative endometriosis recurrence change in endometriosis-related pain.	Sub-analysis GnRHa See SOF table IV.Id		
(Zakhari, *et al.*, 2020b)	systematic review and meta-analysis	Endometriosis	post-operative hormonal suppression with dienogest	post-operative endometriosis recurrence	See SOF table IV.Id (limited to data from controlled studies)		

Endometriosis subtype

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
Ovarian endometrioma							
(Song, *et al.*, 2018)	meta-analysis	2 RCTS (n=134) (endometrioma)	LNG-IUS versus other treatments as a postoperative maintenance therapy	Recurrence	See SOF table IV.1c		
(Vercellini, *et al.*, 2010b)	Systematic review	250 patients assumed long-term oral contraceptive, from one prospective cohort study and one RCT	A literature review including English language medical papers published in the period 1990–2009	Incidence of post-operative endometrioma recurrence in long-term (⩾2 years) oral contraceptive users compared with non-users	A recurrent endometrioma developed in 26/250 women who regularly used oral contraceptive post-operatively (10%; 95% CI 7–15%) compared with 46/115 who did not use oral contraceptive (40%; 95% CI 31–50%), with a common OR of 0.16 (95% CI 0.04–0.65)	Long-term oral contraceptive use until pregnancy is desired should be considered in order to reduce anatomical recurrence of endometrioma	
(Muzii, *et al.*, 2016b)	Systematic review and metanalysis	557 evaluated patients 496 patients completed the assigned treatment and scheduled follow-up (343 had endometriomas)	4 articles (3 RCTs and 1 prospective cohort trial) published through December 2014 comparing the efficacy of 1. Continuous OC regimen (156 pts) 2. Cyclic OC regimen (187 pts) Follow-up varying between 6 and 24 months after surgery	**Primary outcomes** - Recurrence of endometrioma (at TVUS) - Recurrence of pain (either dichotomus or continuous variable) - (dysmenorrhea, noncyclic chronic pelvic pain, dyspareunia) **Secondary outcomes** - Discontinuation of treatment due to side effects - Reoperation rates	**Primary outcomes:** • Recurrence of endometrioma was not significantly different after a continuous vs cyclic OC schedule **(RR 0.54, 95%CI 0.28-1.05, P = .07)**, with low heterogeneity for comparison. • Pain recurrence rate. Continuous OCs were associated with a significantly **lower RR for dysmenorrhea recurrence (RR 0.24; 95% CI 0.06-0.91; p = .04)**, high heterogeneity for comparison. After excluding the nonrandomized trial, statistically significance was not reached for lower RR of dysmenorrhea after continuous OCs **(RR 0.10, 95% CI 0.00-2.70, p = .17)**.	Continuous OCs regimen appears more efficacious to prevent dysmenorrhea recurrence, whereas nonsignificant differences were highlighted for noncyclic pelvic pain and dyspareunia. There is a trend towards lower cyst recurrence rates for a continuous OC regime compared to a cyclic one, but statistical significance was not reached. No conclusive evidence due to the small number of included studies.	

				- Patient satisfaction and QoL	• Nonsignificant differences were found **for chronic pelvic pain (RR 0.61; 95% CI, 0.36-1.03; P = .06) and dyspareunia (RR, 0.77; 95% CI, 0.52-1.12; P = .17)** **Secondary outcomes:** • **Discontinuation rates** similar between continuous vs cyclic treatment (RR, 1.74; 95% CI, 0.83 - 3.64; P = .14) • **Reoperation rates** were similar between the two schedules (RR, 0.53; 95% CI, 0.16 - 1.74, P = .30) • **Patients satisfaction** comparable between the two groups.		
Deep endometriosis							
(Koga*, et al.*, 2015) and (Donnez and Squifflet, 2010).	Non-systematic review	2346 women undergone surgery for ovarian and/or deep infiltrating endometriosis, from 14 studies	The search was limited to peer reviewed, full text articles in the English language published between January 1990 and July 2015.	Prevention of postoperative recurrence of endometriosis related symptoms and endometriotic lesions.	For deep endometriosis: 1 prospective study (Donnez and Squifflet, 2010) showed an overall recurrence rate of 7% after surgical management 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	Continuous OC is more efficacious than cyclic OC, especially for dysmenorrhea. The LNG-IUS is also shown to prevent recurrence of dysmenorrhe. Dienogest, is shown to reduce the recurrence of endometrioma. Long-term medication after surgery for deep infiltrating seems important, although data are limited. Regardless of the lesion and the medication type, patients who discontinued medication experienced a higher incidence of recurrence. In conclusion, regular and prolonged medication until the patient wishes to conceive is highly recommended to prevent the postoperative recurrence of endometriosis.	

INCLUDED AS BACKGROUND INFORMATION
(Abou-Setta*, et al.*, 2006, Vercellini*, et al.*, 2008) (Seracchioli*, et al.*, 2010)

EVIDENCE TO RECOMMENDATIONS – Endometriosis in general

The evidence (and its quality)	THe efficacy of OCP is documented for dysmenorrhea, but 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 symptom recurrence. For LNG-IUS, evidence shows a positive effect on postoperative pain, disease recurrence, and patients' satisfaction after surgery for endometriosis-associated pain. Quality of evidence: ⊕⊕◯◯
Balance between desirable and undesirable outcomes	Benefit with regards to disease / symptom recurrence should be weight against side effects of medical treatments
Balance between different outcomes	For OCP : benefit with regards to dysmenorrhea, side-effects are limited For LNG-IUS ; benefit with regards to postoperative pain and disease recurrence, side-effects are limited No evidence to support particular treatments over others, so they are both options to be discussed with the patient. Balance is different in women seeking pregnancy after surgery, as hormone treatments will cause a delay, and hence these treatments are more appropriate in women not immediately seeking conception
Patient values and preference	Studies showed that LNG-IUS had a positive effect on patient satisfaction after surgery for endometriosis-associated pain. No evidence for OCP, although a generally well accepted treatment
Resource use, equity, acceptability and feasibility	Combined oral contraceptives, preferably in a continuous regimen, and progestins (LNG-IUS) can be considered feasible options as first-line treatments. Prolonged use of hormone therapy is usually feasible but associated with costs and with possible side effects.
RECOMMENDATION	**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.**

EVIDENCE TO RECOMMENDATIONS – Ovarian endometrioma

The evidence (and its quality)	In general post-op hormonal treatment is considered beneficial with regards to symptom recurrence. (see above) Specifically for endometrioma, the evidence on OCP is derived from 1 review including one prospective cohort study and one RCT, showing benefit of OCP use (>2 years) with regards to endometrioma recurrence (Vercellini*, et al.*, 2010b). Similarly, the evidence for LNG-IUS is based on 2 RCTs with a total of 134 patients (Song*, et al.*, 2018). Quality of evidence: ⊕◯◯◯
Balance between desirable and undesirable outcomes	Benefit with regards to disease / symptom recurrence should be weight against side effects of medical treatments
Balance between different outcomes	Risk of hormone therapy are rare and related to specific clinical conditions. Although with limited evidence, there seems to be a benefit of hormone treatment.

	No evidence to support particular treatments over others, so they are both options to be discussed with the patient. Balance is different in women seeking pregnancy after surgery, as hormone treatments will cause a delay, and hence these treatments are more appropriate in women not immediately seeking conception
Patient values and preference	Studies showed that LNG-IUS had a positive effect on patient satisfaction after surgery for endometriosis-associated pain. No evidence for OCP, although a generally well accepted treatment
Resource use, equity, acceptability and feasibility	Prolonged use of hormone therapy is usually feasible but associated with costs and with possible side effects.
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.

EVIDENCE TO RECOMMENDATIONS - deep endometriosis

The evidence (and its quality)	In general post-op hormonal treatment is considered beneficial with regards to symptom recurrence. (see above) Specifically for deep endometriosis, long-term administration of postoperative hormone treatments seems to prevent recurrence of endometriosis-associated symptoms (based on a single prospective study with 500 women) Quality of evidence: ⊕○○○
Balance between desirable and undesirable outcomes	Benefit with regards to disease / symptom recurrence should be weight against side effects of medical treatments
Balance between different outcomes	Benefits include a reduction of recurrence of endometriosis-related symptoms while effects on recurrence of DE lesions are still debated; Risks of hormonal therapy are rare and related to specific clinical conditions. Hence a weak recommendation in favor of treatment. Balance is different in women seeking pregnancy after surgery
Patient values and preference	Unclear
Resource use, equity, acceptability and feasibility	Prolonged use of hormone therapy is usually feasible but associated with costs and with possible side effects.
RECOMMENDATION	For the prevention of recurrence of deep endometriosis and associated symptoms, long-term administration of postoperative hormone treatment can be considered.

ART and endometriosis recurrence

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Somigliana, *et al.*, 2019)	Systematic review	1007 women who postoperatively underwent ovarian stimulation, from 16 studies (4 case reports and 12 observational studies, of which 5 prospective and seven retrospective).	The research was conducted for the period from January 1990 to January 2018	Risk of recurrence of endometriosis in women undergone IVF. Main outcomes were progression (worsening of pain symptoms or growth of endometriotic lesions) or recurrence (onset of new pain symptoms, new lesions, need for surgery o initiation of medical therapy)	Not applicable	IVF does not worsen endometriosis related symptoms; IVF does not increase the risk of endometriosis recurrence (moderate quality evidence)	

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	Moderate quality from a systematic review of observational study and case reports concludes that ART was not associated with increased endometriosis recurrence rate. Quality of evidence: ⊕⊕⊕◯
Balance between desirable and undesirable outcomes	Risk related to ART treatments in general and specific for women with endometriosis versus the benefits of ART with regards to increased pregnancy rate
Balance between different outcomes	Risks of IVF are rare, in general. Evidence is reassuring with regards to the theoretical risk of recurrence of disease with ovarian stimulation. The risks in general do not outweigh the benefits of ART in patients affected by endometriosis seeking pregnancy.
Patient values and preference	Unclear
Resource use, equity, acceptability and feasibility	ART is widely used but associated with costs and with possible side effects
RECOMMENDATION	**Clinicians can perform ART in women with deep endometriosis, as it does not seem to increase endometriosis recurrence per se.**

QUESTION IV.2 HOW SHOULD PATIENTS WITH REOCCURRING ENDOMETRIOSIS OR RECURRING SYMPTOMS BE MANAGED? IS REPETITIVE SURGERY EFFECTIVE FOR SYMPTOMS ASSOCIATED WITH ENDOMETRIOSIS?

Medical / surgical treatment

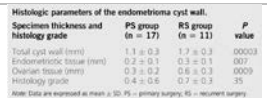
Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Hornstein, *et al.*, 1997)	open-label non randomized cohort study (CS)	36 women age 18-48a with recurrent symptoms after previous successful GnRHagonist treatment within 18 months; surgically confirmed endometriosis; no comparison group, all 36 received GnRHa intranasally; women who completed minimum of 75 days of nafarelin were included in efficacy analyses; exclusion of other hormonal treatments since previous GnRH therapy	3 months of intranasal GnRHagonist nafarelin 200ug twice daily; baseline exam and BMD with DEXA, repeated 3 months after cessation of treatment (6m after baseline) and 9 months after cessation of treatment; 6 visits after cessation of medication at 3 month intervals until 15 months after final dose	Symptom assessment at Baseline and monthly visits, patient kept daily symptom diary; Adverse events (hot flushes), concomitant medications; BMD assessed;	All symptoms significantly improved over treatment period except dyspareunia; by 3 months after cessation of treatment symptom severity increased to that at treatment end but was still better than at baseline ($p<0.001$ for symptom improvement, $p=0.020$ for dyspareunia (NS) over 3 months) BMD did not decrease significantly over the 3 months of treatment (0.56%) but did decrease significantly over the time period of both studies; 81% patients had hot flushes and most other additional adverse events (headache, sinusitis, back pain)		Low (Observational study, no comparison group, small sample size)
(Lee, *et al.*, 2018)	CS (retrospective)	121 women with surgically confirmed endometriosis and previous cystectomy treated with DNG 2mg at detection of recurrence; recurrence defined as newly developed dysmenorrhea or pelvic pain or new endometrioma of minimum 2cm, No comparison group	DNG 2mg given to women with recurrence who had no hormonal treatment in past 6 months; 57 weeks of DNG treatment	Outcomes: pain symptoms, CA-125, Ultrasound findings, and adverse events monitored at 6 month intervals; Primary outcome was change in VAS symptoms; secondary outcomes were change in endometrioma size and CA-125 level between baseline and following DNG treatment	Pain Score decreased from before to 24 weeks and 48 weeks after DNG; Endometrioma size decreased, CA-125 decreased; 42% patients reported adverse events, most common being irregular bleeding $p<0.001$ for baseline symptoms to 24 and 48 weeks post-treatment; $p<0.01$ for decrease in size of endometrioma; $p<0.01$ for CA-125 decrease from baseline to 24 weeks	DNG is effective in reducing the size of endometriomas and serum CA-125 levels along with symptomatic relief and tolerable safety profiles in women with recurrent endometriosis	Low (Observational study, medium size sample, no comparison group)
(Razzi, *et al.*, 2007)	RCT	40 women with recurrent dysmenorrhea and/or pelvic pain after conservative surgery	**desogestrel** (75 mg/d) (n = 20) versus a **combined oral contraceptive** (ethinyl estradiol 20 mg plus desogestrel 150 mg)	VAS score	Sign decrease compared to baseline VAS (in both groups) No difference between groups	Both desogestrel and an oral estro-progestinic were effective, safe and low cost therapy of pain symptoms after endoscopic	

			6 month continuous treatment		No diff in serum CA125, fasting blood glucose, cholesterol and triglycerides levels during treatment. Side effects were reported with the use of desogestrel (breakthrough bleeding 4/20) and pill (body weight increase 3/20).	surgery for endometriosis, the former showing an impact on breakthrough bleeding, the later an incidence on body weight increase.	
(Abdou, *et al.*, 2018)	RCT	242 women aged 20–45 years with recurrent pelvic pain within 1 year following laparoscopic surgery	**dienogest versus depot LA depot leuprolide acetate** (LA) 12-week	VAS for pelvic pain VAS for back pain VAS for dyspareunia Endometrioma size Drug-related adverse effects	No difference at 12 weeks No difference at 12 weeks No difference at 12 weeks No difference at 12 weeks Less hot flushes/vaginal dryness with DNG, less vaginal bleeding/weight gain with LA	Daily dienogest is as effective as depot LA for relieving endometriosis-associated pelvic pain, low back pain and dyspareunia. In addition, dienogest has acceptable safety, tolerability and lower incidence of hot flushes	
(Koshiba, *et al.*, 2018)	Cohort study	146 patients treated for endometrioma After laparoscopic cystectomy using the stripping technique, opening of cul-de-sac obliterations and complete resection of the DE lesions, the patients either received no treatment (n=83), OCP (n=32) or dienogest (DNG; n=27), depending on their medical history. 4 patients excluded because they changed their regimens. All patients were followed up every 3 months.	16 patients developed a recurrence of the endometrioma (12 in the nontreatment group, three in the OC group and one in the DNG group). - 11 treated with **DNG** immediately after the diagnosis of recurrent endometrioma. - 3 patients received OC - 1 patient underwent secondary surgery - 1 no additional treatment (attempting pregnancy)		Among the 11 DNG patients: - 7 DNG (2 mg) for 24 months. After 24 months of treatment with DNG, complete resolution of recurrent endometrioma was achieved in 4 (57.1%) of 7 patients. - 4 stopped DNG (side effects, conception, shorter FU) Among 3 OC patients, and 1 sec surgery: - No improvement	DNG therapy early after recurrence of postsurgical endometrioma appears to be viable for reducing the risk of repeated surgery.	
(Vercellini, *et al.*, 2002)	Cohort study	90 women with recurrent moderate or severe pelvic pain after conservative surgery for symptomatic endometriosis Mean (±SD) time to pain recurrence from first-line surgery was 8 ± 2 months in the cyproterone group and 9 ± 3 months in the oral contraceptive group.	6 months of continuous treatment with **oral cyproterone acetate**, 12.5 mg/d, or an oral **contraceptive** containing ethinyl estradiol, 0.02 mg, and desogestrel, 0.15 mg.	Satisfaction symptom scores (VAS and verbal rating scales (VRS))	73% of subjects in the cyproterone acetate group were satisfied or very satisfied after 6 months of treatment compared with 67% in the OCP group (OR 1.37 [95% CI, 0.56 to 3.40]) A substantial decrease was observed in all symptom scores (VAS + VRS) in both study arms; between-group differences were not significant. At 6 months of treatment, 5 patients in the	Both cyproterone acetate and a continuous monophasic oral contraceptive were effective, safe, and inexpensive therapy for recurrent pain after conservative surgery for endometriosis. Both cyproterone acetate and a continuous monophasic oral contraceptive were effective, safe, and	

				Side effects	cyproterone acetate arm and 6 in the OCP arm still reported at least one moderate or severe pain symptom on both scales. 7 women taking cyproterone acetate experienced substantial reduction in libido. The main side effects causing withdrawal from the study were bloating (n=1), decreased libido (n=1), depression (n=1), and headache (n=1) in the cyproterone acetate group and weight gain (n=2), headache (n=1), and nausea (n=1) in the OCP group.	inexpensive therapy for recurrent pain after conservative surgery for endometriosis.	
(Candiani, *et al.*, 1991)	Observational study (no control group)	42 women with recurrent endometriosis (confirmed with histology) Mean age 31.1 ± 4.3 y	Repetitive conservative surgery (with or without pre- or postoperative medical treatment)	Pain symptoms (Pregnancy) Need for a third operation Mean follow up 41.8 ± 30.3 months Mean time between operations; 47.9 ± 28.8 months	Dymenorrhea returned in 8 (19%) women, pelvic pain in 7 (17%) In 6 women (14%) – due to reappearance of symptoms and signs - after 21, 28, 33, 35, 39 and 54 months.	Conservative surgery is an effective therapeutic option for infertile patients with recurrent endometriosis.	
(Muzii, *et al.*, 2015)	Prospective controlled study	Consecutive patients with pelvic pain and/or infertility undergoing laparoscopic excision of a monolateral ovarian endometrioma for the first time (17 patients) or for recurrence after previous surgery (11 patients).	Second surgery for endometrioma vs first surgery	Cyst wall histologic evaluation ovarian reserve with AFC and ovarian volumes of both the operated and contralateral, non-operated ovary FU : 3 months	 Histologic parameters of the endometrioma cyst wall. Specimen thickness and histology grade / PS group (n = 17) / RS group (n = 11) / P value Total cyst wall (mm) 1.1 ± 0.3 1.7 ± 0.3 .0003 Endometriotic tissue (mm) 0.2 ± 0.1 0.3 ± 0.1 .007 Ovarian tissue (mm) 0.3 ± 0.2 0.6 ± 0.3 .0009 Histology grade 0.4 ± 0.6 0.7 ± 0.3 .35 Note: Data are expressed as mean ± SD. PS = primary surgery; RS = recurrent surgery. AFC 1st surgery; 5.1 ± 2.8 2nd surgery : 3.5 ± 1.4 P=0.07 Ovarian volume (ml) 1st surgery; 7.0 ± 2.0 2nd surgery : 5.3 ± 1.7 P=0.03	Excisional surgery for recurrent endometriomas appears to be associated with histologic evidence of higher loss of ovarian tissue if compared with primary surgery, and may be more harmful to the ovarian reserve as evaluated by AFC.	

INCLUDED AS BACKGROUND INFORMATION
/

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	Direct evidence of efficacy is only available for GnRH agonists and dienogest. Quality of evidence: ⊕◯◯◯ (based on four small observational studies – nafarelin, dienogest x 2, letrozole)

	There is no evidence that hormonal treatment has a negative/positive effect on further disease progression
Balance between desirable and undesirable outcomes	The benefits of different interventions should be weighted against their side-effects.
Balance between different outcomes	In general, treatments in endometriosis are considered to have limited risks and therefore the possible benefits may outweigh the risks. GnRH agonists and antagonists could have more side effects and possible harms, as well as repeated Surgery Balance is different if the woman wishes to become pregnant. Although evidence of benefit is only available for few selected treatments, it was considered that this 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 other sections of the guideline.
Patient values and preference	Shared decision-making approach recommended
Resource use, equity, acceptability and feasibility	Consider costs of each approach and availability (different across countries) Hormonal treatment may be indicated for contraception anyway
RECOMMENDATION	**Any hormone treatment or surgery can be offered to treat recurring pain symptoms. in women with endometriosis**

QUESTION V.1 WHICH DIAGNOSTIC PROCEDURES SHOULD BE APPLIED IN ADOLESCENTS WITH POSSIBLE ENDOMETRIOSIS?

Diagnostic process / Risk factors for adolescent endometriosis

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Geysenbergh, *et al.*, 2017)	systematic review	sample size 104-1721	A systematic review of literature and quality assessment was performed in order to identify questionnaires that were developed to identify adult women with endometriosis. Based on these questionnaires, specific questions that had been reported to be predictive for endometriosis were selected and included in a newly composed questionnaire with the aim to identify adolescents at risk of developing endometriosis.	diagnosis of endometriosis in adult women	Based on the literature, we identified 5 questionnaires developed to identify adult women with endometriosis; this questionnaire contained 6 questions that had been reported to be predictive for adult endometriosis. These questions query age of menarche, cycle duration, dysmenorrhea, pain descriptors, dyschezia and urinary symptoms and were combined into a new self-report questionnaire aimed to identify adolescents at risk to develop endometriosis.	We developed a self-report questionnaire aimed to identify adolescents at risk to develop endometriosis based on questions from self-report questionnaires that have been reported to identify adult women with endometriosis.	
(Shah and Missmer, 2011)	narrative review	n/d	n/d	n/d	Research on adolescent endometriosis is still in its infancy, and the existing publications are of case series and descriptive studies. It is possible that the disease has a different pathophysiology in the adolescent population, but little epidemiologic or molecular data exist to support or refute this speculation. Case-control and cohort studies to identify risk factors for adolescent endometriosis during the in utero, early childhood, and pubertal time periods are crucial to advance our understanding of disease etiology and progression. In addition, the limited literature does not yet confirm that intervening in the adolescent population prevents long-term sequelae such as pain and infertility as adults. Other areas for investigation include the efficacy of GnRH-agonists with or without add-back therapy in adolescents, as well as long-term follow-up studies of disease progression and quality of life with medical versus surgical treatment. The short- and long-term impact of diet, lifestyle, and complementary and alternative therapies is also in need of formal investigation. Prospective observational and intervention studies are required to address many of these enduring questions about endometriosis in the adolescent population		short review, not systematic, but relevant for PICO (considered more as background information)

(Chapron, *et al.*, 2011)	cross-sectional study	non-deep endometriosis n=131 (superficial peritoneal and ovarian endometrioma), deep-invasiVe n=98. age 17-41, histologIcally confirmed endometriosis. ASRM I: n=41, ASRM II n= 46, ASRM III n= 85, ASRM IV n=57	questionnaire about medical history, family history and symptoms	deep endometriosis or non-deep (superficial or endometrioma) endometriosis diagnosed later in life	accuracy: VAS >7: OR (95% CI) dysmenorrhoea 2.8 (1.6-4.6), deep dyspareunia 2.5 (1.2-5.5), non cyclic chronic pelvic pain 3.5 (1.2-10.3), gastro intestinal symptoms 8.6 (3.4-21.7); prescription of OC because of severy primary dysmenorrhoea: age <18: 4.2 (1.8-10.0)	predictive markers for later deep endometriosis are family history of endometriosis, absenteism from school during menses, early and prolonged use of OC because of dysmenorrhoea. Treatment with NSAIDs should be started and if not effective, surgery should be considered	authors look at adults with endometriosis and look back in order to predict DIE.
(Vicino, *et al.*, 2010)	*See below*						
(Brosens, *et al.*, 2013)	*See below*						
(Treloar, *et al.*, 2010)	*See below*						
(Vicino, *et al.*, 2010)	*See below*						

INCLUDED AS BACKGROUND INFORMATION
(Greene, *et al.*, 2009).

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	The evidence to predict endometriosis based on clinical symptoms alone is weak and incomplete. In women seeking help from general practitioners, a number of signs and symptoms were shown to be associated with a diagnosis of endometriosis. The guideline group suggests to consider these signs and symptoms for a diagnosis of endometriosis. Quality of evidence : ⊕○○○ (Chapron, *et al.*, 2011, Geysenbergh, *et al.*, 2017)
Balance between desirable and undesirable outcomes	Benefit: Earlier detection and ruling out of a common and costly disease hopefully leading to less suffering and better treatment outcomes Risks: Incorrect diagnosis - Overtreatment
Balance between different outcomes	It was considered that focus would be on identifying women for further diagnostic work-up rather than missing diagnosis of endometriosis due to unspecific/unfamiliar symptoms. 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.
Patient values and preference	No data

Resource use, equity, acceptability and feasibility	To take a carefull history and be mindful of risk factors for endometriosis is considered an acceptable recommendation
RECOMMENDATION	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.
RECOMMENDATION	Clinicians may consider endometriosis in young women presenting with (cyclical) absenteeism from school, or with use of oral contraceptives for treatment of dysmenorrhea.

Clinical symptoms

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Greene, *et al.*, 2009)	Cross sectional study of self reported data	4334 women with surgically confirmed endometriosis	being seen by medical doctor	specialty of first physician seen, timing of onset of symptoms, time to seeking medical help and to diagnosis, number of physicians seen, satisfaction with care	adolescents were more likely to see a generalist first (adjusted OR 1.31, 95% CI = 1.14-1.51; p=0.0002); adolescents waited three times as long to seek medical attention (6.0 +- 0.2 yrs) than adults (2.0 +- 0.3 yrs) (p<0.001) ; mean time to diagnosis in adults after seeking help was 4.7 +- 0.1 yrs at an average of 29.6 +-0.1 yrs. Time to diagnosis after seeking help in adolescents was 5.4 +-0.2 yrs, adolescents had diagnosis at younger age than adults (28.8 +- yrs compared to 30.7 +-0.1yrs, p<0.0001). Adolescents did not see more or less physicians compared to adults; 69.6 vs 49.8% of adolescents compared to adults were told nothing was wrong (adjusted OR 2.26 95% CI 1.97, 2,59; p<0.0001; adolescents reported not being taken seriously in 65.2% compared to 48.9% of adults, adjusted OR 1.95, 95% CI1.69, 2.24, p<0.0001.	in adolescents as compared to adults: adolescents waited longer before seeking help, had a longer time to diagnosis, were more likely to report not being taken seriously, higher chance of being told nothing was wrong. Especially adolescents are dependent on their physicians (and their parents) in recognizing that they are ill	recognition problem in adolescents: relevant for PICO question
(DiVasta, *et al.*, 2018)	Cross-sectional study	final sample of 402 endometriosis cases. Among these participants, 202 completed the first version of the questionnaire, and 200 completed the expanded World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonization	surgically confirmed diagnosis of endometriosis	time to diagnosis, menstrual complaints, number of doctors seen	diagnosis; menstrual symptoms; acyclic pain; urinary tract and gastro intestinal symptoms: dysmenorrhoea and acyclical general CPP were comparable between adults and adolescents.	Pelvic pain was severe and noncyclic and negatively impacted quality of life. At our tertiary care centers, symptoms of endometriosis did not differ between women surgically diagnosed during adolescence compared with those diagnosed as adults. Adolescents had more nausea and symptom onset at menarche. Multi-year delays in	relevant for diagnostic process

		Project standard clinical questionnaire. Participants ranged in age from 12e49 years old at enrollment (median age, 19 years. Adolescents were defined as <=18 years				diagnosis were common. Clinicians should be aware of these alternate symptom patterns and include endometriosis in their differential diagnosis for both adolescent and young adult women who experience noncyclic pelvic pain and nausea.	
(Treloar*, et al.*, 2010)	Case control	n= 268 women with surgically confirmed moderate-severe endometriosis, n= 244 women without endometriosis (controls)	early menstrual characteristics, before time of onset of endometriosis	age of menarche, tampon use, history of dysmenorrhoea, duration of menstrual cycle, heaviness of bleeding, sexual intercourse during menstruation	Menarche after 14 years is strongly and inversely associated with endometriosis (OR 0.3%, 95% CI 0.1-0.6); history of dysmenorrhoea is associated with endometriosis (OR 2.6, 95% CI 1.1-6.2)	Decreased risk of endometriosis with late age of menarche, increased risk in women reportin early history of dysmenorrhoea	early menstrual characteristics are relevant for diagnostyic process
(Vicino*, et al.*, 2010)	Prospective clinical study	38 women <21 yrs	laparoscopy	endometriosis and stage. The mean age at diagnosis was 18.6 years, except in 3 cases (7.9%) in which it was made at ≤ 15 years of age. None of the patients had a prior diagnosis of genital malformations, nor were any cases of diagnosed familiarity for endometriosis. Pelvic pain was present in all cases, although in 3 cases the presence of a pelvic mass was the indication for surgery.	symptoms related to findings on laparoscopy	The main clinical finding emerging from this analysis suggests that pelvic pain is the main symptom. In our series pain was present in all cases and an ovarian endometrioma was present in three cases. With regard to the stage and site of the disease, the frequency of minimal-mild endometriosis was lower than in adult cases observed in the experience of GISE.	not really about diagnostic process, but informative about adolescents
(Yang*, et al.*, 2012).	*See below*						

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	From 1 high and 3 low quality articles, it can be concluded that a more varied pain pattern is seen in adolescents with endometriosis as compared to adults. The evidence to predict endometriosis based on clinical symptoms alone is weak and incomplete. In women seeking help from general practitioners, a number of signs and symptoms were shown to be associated with a diagnosis of endometriosis. The guideline group suggests to consider these signs and symptoms for a diagnosis of endometriosis. Quality of evidence : ⊕◯◯◯ (observational data only)
Balance between desirable and undesirable outcomes	Desirable outcomes: to estimate chance of endometriosis correctly based on reliable signs and symptoms Undesirable outcomes: to reject or confirm the diagnosis uncorrectly

Balance between different outcomes	The benefits of comprehensive history taking the benefits outweigh the risks
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	History taking is cheap, acceptable and feasible but has to be comprehensive because the pattern of signs and symptoms is more extensive/varied in adolescents than in adults with endometriosis
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 , dysmenorrhea, dyschezia, dysuria, dyspareunia** **- cyclical pelvic pain.**

Findings during examination, ultrasound

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Brosens, *et al.*, 2013)	OPINION ('review')	12 articles, total of 437 patients with laparoscopic proven endometriosis	different for every included study	n/a	n/a	1.TVE should be performed in order to diagnose ovarian endometrioma in early stage. 2. hydrolaparoscopy in order to diagnose peritoneal (and deep) endometriosis because it is better accepted and less invasive than conventional laparoscopy.Early onset of chronic pelvic pain is risk factor for severe endometriosis in adolescence. TVE in order to diagnose ovarian endometriosis and hydrolaparoscopy to diagnose peritoneal and deep. Hydrolaparoscopy less invasive and more accepted than conventional laparoscopy 6,5 to 40.2% of girl with (obstructive) genital tract anomaly have endometriosis (Dovey and Sanfilippo 2010)	
(Yang, *et al.*, 2012)	retrospective review of medical records	63 patients<20 years with surgical diagnosis of endometriosis	clinical presentation, auxilliary examinations, surgical outcomes and post-operative medical treatment	CA125 increased in 80,4% and positive ultrasound in 87,3%	Mean age of diagnosis : 18,4 - Earlier if genital tract malformation	Multiple sites lesions found in operation was a risk factor of recurrence. GnRHa was effective to prevent the recurrence.	US has to be suggested for endometriosis. High percentage of genital tract malformation in adolescents with endometriosis.

(Martire*, et al.*, 2020)	Retrospective observational study.	270 women aged 12–20 years	2D, 3D, and power Doppler US pelvic examination (transvaginal or transrectal in pre–sexually active adolescents)	All possible locations of endometriosis evaluated and recorded using a dedicated US mapping sheet and severity of painful symptoms evaluated through VAS	Dysmenorrhea was detected in 147 (54.4%) of 270 patients and heavy menstrual bleeding in 76 (28.1%) of 270. At least one ultrasound feature of endometriosis was identified in 36 (13.3%) of 270 cases. Ovarian endometriomas were found in 22 (11%) patients, adenomyosis in 16 (5.2%), and DE in 10 (3.7%). US signs of endometriosis were found in 21% of adolescents who reported dysmenorrhea and 33% with dyspareunia. The presence of DE at US was associated with bowel symptoms in 33% of patients and associated with dyspareunia in 25% of patients.	The detection rate of pelvic endometriotic lesions at ultrasound was 13%. The rates of dysmenorrhea, dyspareunia and heavy menstrual bleeding in adolescents with endometriosis ultrasound signs were statistically significantly higher compared with those without. In patients with dysmenorrhea, the detection rate of pelvic endometriosis at ultrasound increased to 20%.	

INCLUDED AS BACKGROUND INFORMATION
(Nisenblat*, et al.*, 2016b)

EVIDENCE TO RECOMMENDATIONS – clinical examination

The evidence (and its quality)	No evidence was found with regard to clinical examination in adolescents. Quality of evidence: NA
Balance between desirable and undesirable outcomes	Desirable outcome: early diagnosis Undesirable outcome: painful and potential psychological harmful examination
Balance between different outcomes	The value of clinical examination for adults with endometriosis has been discussed above. In adolescents, the benefit of clinical examination towards the diagnosis of endometriosis (and/or during the investigative process) should be weighted against the discomfort and possible psychological harms. This assessment should be made on a case-by-case basis (considering age and cultural background), and preceeded by a discussion with the adolescent and her caregiver. This was formulated as a GPP
Patient values and preference	No information
Resource use, equity, acceptability and feasibility	Examination is feasible in general, but specificities of adolescents (such as age and cultural background) may impact on acceptability
RECOMMENDATION	**In the absence of evidence for adolescents specifically, the recommendations for clinical examination in adults can be applied.**
GPP	**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.**

EVIDENCE TO RECOMMENDATIONS – Imaging

The evidence (and its quality)	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.*, 2016b). Quality of evidence : ⊕⊕◯◯ (see above)
Balance between desirable and undesirable outcomes	Desirable outcome: early diagnosis Undesirable outcome: painful and potential psychological harmful examination for adolescents with intact hymen
Balance between different outcomes	Value of positive outcome (endometrioma present) is high: diagnosis is confirmed, thereby outweighing the risk, especially in adolescents whose hymen is not intact
Patient values and preference	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. When Transvaginal ultrasound is not appropriate, alternative options have been included in the recommendation.
Resource use, equity, acceptability and feasibility	Transvaginal ultrasound is relatively inexpensive; easily accessible, well accepted by and feasible for adolescents in whom hymen is not intact.
RECOMMENDATION	**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.**

Laboratory parameters

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Seckin, *et al.*, 2018)	retrospective chart review	502 patients who underwent surgery: 267 with endometriomas (endometrioma group) and 235 with other benign adnexal cysts (control group) Subgroups younger (aged <25 yrs) vs older (aged >/=25 yrs).	Total and differential white blood cell count, neutrophil-to-lymphocyte ratio, platelet indices and platelet-to-lymphocyte ratio (PLR)	clinical value of hematologic markers in the differential diagnosis of endometrioma	The mean serum levels of PLR, plateletcrit (PCT), platelet count and CA-125 (RR below 35 IU/mL): significantly higher in endometrioma group ($p < 0.001$). AUC for CA-125: 0.85 [95%CI 0.82-0.88] ($p < 0.001$) Platelet count, PLR, and PCT showed poor discriminative ability for detecting endometriomas with AUC values of 0.59 (95% CI, 0.55-0.65, p <	Hematologic markers do not adequately differentiate ovarian endometriomas from other benign cysts in neither adolescents/young adults nor older women.	

					0.001), 0.58 (95% CI, 0.53-0.63, p = 0.002) and 0.61 (95% CI, 0.56-0.66, p < 0.001), resp. In subanalysis; platelet indices had low diagnostic performance in both age groups		
(Sasamoto, *et al.*, 2020).	cross-sectional study	adolescents and young women with and without surgically-confirmed endometriosis (n=282) 95% rASRM stage I/II controls (n=293) Median age at blood draw was 24 years in controls and 17 years in cases	Plasma CA125	Correlation with type of endometriosis and severity of pain	Average CA125 : 12.5 U/mL in controls and 12.1 U/mL in cases CA125 did not differ by pain type, its severity, or frequency in endometriosis cases or controls. Among participants who reported dysmenorrhea, CA125 did not discriminate endometriosis cases from controls using cutoff of 35 U/mL (AUC = 0.51, 95%CI = 0.50–0.53). Among adolescents and young adult women, CA125 did not correlate with pain type.	CA125 did not efficiently discriminate endometriosis cases from controls	

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	One moderate quality study which concluded that serum biomarkers do not adequately differentiate ovarian endometriomas from other benign cysts in neither adolescents nor older women. In adults, evidence is available from high quality systematic reviews and meta-analysis (based on low to moderate quality studies). Quality of evidence: ⊕⊕⊕◯ 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).
Balance between desirable and undesirable outcomes	Benefit: A non-invasive, cost-effective and reliable approach to rule in/out endometriosis would allow for individualized treatment and reduce uncertainty and unnecessary investigations and treatment attempts. Risks: Sensitivity/specificity is not sufficient for the different tests to replace invasive diagnostic tests in clinical practice.
Balance between different outcomes	The benefits of a non- or minimally invasive tests would be preferable, but no biological markers currently exist that reliably can rule in and/or rule out endometriosis.
Patient values and preference	Patients are expected to prefer non- or minimally invasive tests for diagnosing endometriosis
Resource use, equity, acceptability and feasibility	NA as the serum markers described do not discriminate. Non- or minimally invasive tests (if they would be available) are considered more acceptable and feasible than invasive tests/procedures.

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

Diagnostic laparoscopy

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Shah and Missmer, 2011)	*See above*						
(Brosens, *et al.*, 2013)	*See above*						
(Vicino, *et al.*, 2010)	*See above*						
(Yang, *et al.*, 2012)	*See above*						

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	1 moderate quality review concludes that nearly two-thirds of adolescents with CPP or dysmenorrhea have laparoscopic evidence of endometriosis Quality of evidence: ⊕⊕◯◯
Balance between desirable and undesirable outcomes	Desirable outcome: diagnosis confirmed Undesirable outcome: riskful and painful procedure (surgery), postoperative complications
Balance between different outcomes	In general, the risks of laparoscopy do not outweigh the benefits, and possible diagnostic laparoscopy should be avoided by confirming the diagnosis by history and ultrasound, or proceeding to empirical treatment. In adolescents where other diagnostic options cannot be used or have failed, or if medical treatments (empirical) have not been successful, the benefits of laparoscopic confirmation may outweigh the risks. One further difficulty is that some reports suggests that peritoneal endometriosis in adolescents may have atypical appearance, which may further complicate laparoscopic diagnosis and limit its value.
Patient values and preference	No data

Resource use, equity, acceptability and feasibility	Diagnostic laparoscopy is expensive, but accessible and feasible if other options have failed. Treatment should not be withheld for adolescents in which laparoscopic diagnosis was not (yet) performed.
RECOMMENDATION	**In adolescents with suspected endometriosis where imaging is negative and medical treatments (with NSAIDs and/or oral contraceptives) have not been successful, diagnostic laparoscopy may be considered .**

QUESTION V.1B SHOULD DIAGNOSIS OF ENDOMETRIOSIS IN ADOLESCENTS BE CONFIRMED BY HISTOLOGY?

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Janssen, *et al.*, 2013)	systematic review	n=880 girls 10-21 yrs, undergoing laparoscopy. Main symptom was CPP, CPP resistant to pain medication, or dysmenorrhoea	laparoscopy some with histology	The primary outcome measure was the prevalence of laparoscopically confirmed endometriosis in adolescent girls. The classification of endometriosis was a secondary outcome measure	62% of girls had visually confirmed endometriosis at laparoscopy	About two-thirds of adolescent girls with CPP or dysmenorrhea have laparoscopic evidence of endometriosis. About one-third of these adolescents with endometriosis have moderate–severe disease. The value of early detection of endometriosis in symptomatic adolescents and the indications for laparoscopic investigation in adolescents require more research	authors used CPP in search terms, so they looked for CPP as a symptom and not for other symptoms. Possible selection bias.

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	One moderate quality review concludes that histological confirmation rate of suspected endometriosis at laparoscopy is high (93%). Quality of evidence: ⊕⊕○○
Balance between desirable and undesirable outcomes	Desirable outcome: confirmed endometriosis, no malignancy Undesirable outcome: complication because of procedure
Balance between different outcomes	The high rate of histological proven endometriosis confirms that endometriosis may easily be recognized macroscopically. However because of the varying patterns of adolescent endometriosis it may be useful to take biopsies
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	Diagnostic laparoscopy with histology is expensive, but accessible and feasible
RECOMMENDATION	**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.**

QUESTION V.2 WHAT IS THE BEST TREATMENT FOR ADOLESCENTS WITH (SUSPECTED) ENDOMETRIOSIS?

Medical treatment

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Davis, *et al.*, 2005).	RCT	76 healthy adolescents aged 19 years or younger reporting moderate or severe dysmenorrhea.	Subjects were randomly allocated to receive either an OC (ethinyl estradiol [E2] 20 microg and levonorgestrel 100 microg) or a matching placebo for 3 months. Participants used their usual pain medications as needed during the trial.	The main outcome measure was score on the Moos Menstrual Distress Questionnaire (pain subscale) for the third menstrual cycle on treatment. Secondary outcomes included pain intensity (rated 0 to 10), days of any pain, days of severe pain, hours of pain on worst day, and use of pain medications	The mean Moos Menstrual Distress Questionnaire pain score was lower (less pain) in the OC group than the placebo group (3.1, standard deviation 3.2 compared with 5.8, standard deviation 4.5, P = .004, 95% CI for the difference between means 0.88-4.53). By cycle 3, OC users rated their worst pain as less (mean pain rating 3.7 compared with 5.4, P = .02) and used fewer pain medications than placebo users (mean pain pills used 1.3 compared with 3.7, P = .05). By cycle 3, OC users reported fewer days of any pain, fewer days of severe pain, and fewer hours of pain on the worst pain day than placebo users; however, these differences did not reach statistical significance.	Among adolescents, a low-dose oral contraceptive relieved dysmenorrhea-associated pain more effectively than placebo	
(Yoost, *et al.*, 2013)	Retrospective cohort study.	Adolescent patients age 14-22 with pathology-proven endometriosis who had the LNG-IUS placed during the course of their treatment for this disease Pediatric Adolescent Gynecology Clinic and Children's Hospital in a metropolitan area.	Patients were divided into LNG-IUS placement at the time of surgical diagnosis versus placement some time after diagnosis.	Pain and bleeding were assessed by follow-up exam. Pain was classified at each follow-up visit as either none, minimal, moderate, or severe. Bleeding was classified as none, irregular spotting, irregular bleeding, or daily bleeding.	The majority of patients (67%) required additional hormonal therapy for pain and bleeding suppression. Time to bleeding suppression and pain suppression was sooner in the group with interval time between surgical diagnosis and LNG-IUS placement, compared to LNG-IUS placement at the time of surgery (2.4 months vs 5.3 months until bleeding suppression, and 3.8 months vs 4.8 months until pain suppression), although statistical significance was not achieved.	The LNG-IUS is an option for treatment of endometriosis in adolescents. As pain is the main problem associated with endometriosis, LNG-IUS placement is beneficial at the time of surgery when it is diagnosed. A prospective study is needed for further assessment of outcomes.	article is included because only article on LNG-IUS. However very low quality, and outcomes are troubled because patients are using combinations of different medical therapies together with LNG-IUS

(Ebert, *et al.*, 2017).	other	97 patients, no control group, age 12 - below 18, clinical suspected or surgically confirmed endometriosis	52 weeks of dienogest 2 mg once daily	lumbar spine bone mineral density (BMD) at baseline and at end of treatment (EOT), secondary outcomes: pain, quality of life	lumbar BMD decreased at EOT with 1.2%, partially returned within 6 months; VAS: 64.3mm at baseline, 36.8 at week 4, 9.0 at week 48 (VAS at EOT was only presented in supplementary data); EHP-30 improved in all items; 83% of participants had AE (headache, breast discomfort, weight increase, abdominal pain)	Dienogest is effective, effect on pain is similar as in adults	
(Gallagher, *et al.*, 2017)	trial	50 female adolescents (aged 15-22 years) with surgically confirmed endometriosis initiating treatment with GnRHa.	Subjects were randomized to: NA (5 mg/d) with CEE (0.625 mg/d) or NA (5 mg/d) with placebo. All subjects received leuprolide acetate depot every 3 months.	The Short Form-36 v2 Health Survey, Beck Depression Inventory II, and Menopause Rating Scale were completed at repeated intervals.	At baseline, subjects reported impaired physical health-related QOL compared with national norms (all P < .0001). Over 12 months, these Short Form-36 v2 scores improved (all P < .05). Subjects receiving NA with CEE showed greater improvements in the pain, vitality, and physical health subscales (Pbetween groups < .05) than those receiving NA alone, as well as better physical functioning (P < .05). There were no changes in depression or menopause-like symptoms in either group.	Female adolescents with endometriosis initiating GnRHa therapy have impaired QOL. Treatment with GnRHa combined with add-back therapy led to improved QOL, with no worsening of mood or menopausal side effects. NA with CEE was superior to NA alone for improving physical health-related QOL.	article included. GnRHa + NA + CEE results in better QoL than GnRHa + NA alone
(DiVasta, *et al.*, 2015)	randomized double blind placebo controlled study	65 patients, 53 randomized, age 15-22, surgically confirmed endometriosis, using GnRH analogue 11.25 mg per 3 months;	norethindrone acetate (5 mg/day) plus conjugated equine estrogens (NA + CEE) (0.625 mg/day), duration 52 weeks OR NA + placebo	Bone mineral density measured by DEXA scan at 0, 6, 12 months	34 women completed the trial; dropouts did not differ from those who completed the trial. Bone mineral density was normal at baseline. At 12 months, total body bone mineral content and BMD had increased in the NA + CEE group (bone mineral content +37 g, P<.001 and BMD +0.012 g/cm 2, P.05), but not in the NA + placebo group (bone mineral content P.19 and BMD P.95). Lean mass increased only in NA+CEE (+1.4 kg, P.001). Improvements in physical functioning domains of quality-of-life assessments were greater with NA+CEE (P.005). No differences were seen at the hip or lumbar spine by dual-energy X-ray absorptiometry. No significant adverse events occurred.	Hormonal add-back successfully preserved bone health and improved quality of life for adolescents and young women with endometriosis during 12 months of gonadotropin-releasing hormone agonist therapy. Combination norethindrone acetate plus conjugated equine estrogens add-back appears to be more effective for increasing total body bone mineral content, areal BMD, and lean mass than norethindrone acetate monotherapy.	
(Gallagher, *et al.*, 2018)	trial	Female adolescents with surgically confirmed endometriosis (n = 51) who enrolled in a GnRHa	Leuprolide depot 11.25 mg intramuscular injection every 3 months, plus oral norethindrone acetate 5 mg daily or oral	Side effects during and after treatment, irreversible side effects, changes in pain, overall satisfaction.	The response rate was 61% (25 of 41; 10 subjects could not be located). Almost all (24 of 25) reported side effects during treatment; 80% (16 of 21)	Subjects believed that GnRHa used with add-back was effective and would recommend it to others, despite significant side	

		plus add-back trial as adolescents.	norethindrone acetate 5 mg daily and oral conjugated equine estrogens 0.625 mg daily.		reported side effects lasting longer than 6 months after stopping treatment. Almost half (9 of 20) reported side effects they considered irreversible, including memory loss, insomnia, and hot flashes. Despite side effects, participants rated GnRHa plus add-back as the most effective hormonal medication for treating endometriosis pain; two-thirds (16 of 25) would recommend it to others. More participants who received a modified 2-drug add-back regimen vs standard 1-drug add-back would recommend GnRHa and believed it was the most effective hormonal medication.	effects. Those who received 2-drug add-back reported more success than those who received standard add-back. A subset of patients reported side effects they consider to be irreversible.	

EVIDENCE TO RECOMMENDATIONS – NSAIDS / OCP – progestogens

The evidence (and its quality)	No evidence about NSAIDs, moderate quality evidence about OC, low to moderate evidence about progestins, moderate to high quality evidence about GnRH analogues. OC, progestins and GnRH agonists may be effective against pain Quality of evidence: ⊕◯◯◯ (lowest level over all treatments)
Balance between desirable and undesirable outcomes	Desirable outcomes: effective treatment of pain Undesirable outcomes: side effects, unsafety
Balance between different outcomes	The benefits of medical treatment may outweigh the risks, if taken cautiously hormonal treatment may be effective and safe. For progestogen, the possible impact on BMD is highlighted. 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.
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	NSAIDs, COCs, and progestins are relatively cheap and their use is acceptable as they are considered relatively safe
RECOMMENDATION	**In adolescents with severe dysmenorrhea and/or endometriosis-associated pain, clinicians should prescribe oral 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**
GPP	**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.**

EVIDENCE TO RECOMMENDATIONS - GnRH agonists

The evidence (and its quality)	Evidence includes several studies on GnRH antagonists, but mostly comparing efficacy of GnRHa versus GnRHa plus add back therapy and therefore provide only indirect evidence that GnRH agonists may be effective against pain. Quality of evidence: ⊕⊕◯◯
Balance between desirable and undesirable outcomes	Desirable outcomes: effective treatment of pain Undesirable outcomes: side effects, unsafety
Balance between different outcomes	Considering the possible side effects with regards to BMD and other long term health risks associated with GnRH agonist with add-back therapy, it was considered that the benefits of GnRH agonist would only outweigh the harms in patients that failed to respond to other treatments listed as first-line treatments, NSAIDs, oral contraceptives or progestogens). An additional GPP was formulated to strengthen the message for a cautious approach.
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	GnRH agonist are more expensive and should be taken with add back therapy
RECOMMENDATION	**In adolescents with laparoscopically confirmed endometriosis and associated pain in whom oral 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.**
GPP	**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.**

Surgical treatment

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Yeung, *et al.*, 2011)	Prospective observational case series (Canadian Task Force II-3)	20 Teenagers with symptoms suspicious for endometriosis who underwent complete laparoscopic excision of all areas of abnormal peritoneum with typical and atypical endometriosis. 17 patients had endometriosis confirmed by histology at initial surgery.	effect of surgery on endometriosis related p[ain symptoms	Rate of recurrent (or persistent) endometriosis.	There was a statistically significant improvement in most pain symptoms, including bowel-related symptoms, during this time period. The rate of repeat surgery was 8 of 17 patients (47.1%), but the rate of endometriosis (diagnosed visually or histologically) found at surgery was zero. Only one-third of patients took postoperative hormonal suppression for any length of time.	Complete laparoscopic excision of endometriosis in teenagers--including areas of typical and atypical endometriosis--has the potential to eradicate disease. These results do not depend on postoperative hormonal suppression. These data have important implications in the overall care of teenagers, regarding pain management, but also	inclusion, relevant outcomes regarding stage I - II endometriosis

		Follow-up was up to 66 months (average 23.1 months)				potentially for fertility. Further large comparative trials are needed to verify these results.	
(Roman, 2010a)	Comparative cohort study	Patients, including 20 adolescents, with endometriosis treated consecutively between July 2003 and January 2009 with a follow-up between 6 months and 6 years. SETTING: Braemar Hospital, Hamilton, New Zealand.	surgery for endometriosis, comparison adolescents/non-adolescents	pain, analgesics use, recurrence of symptoms	95% (19/20) of adolescents were using pain relief other than Paracetamol, in contrast to only 59% (84/143) of non-adolescents. Thirty per cent (6/20) of adolescents had a first-degree relative with endometriosis, in contrast to 8% (11/143) of non-adolescents. Endometriosis was found to be stage I in 40% (8/20) of patients, stage II in 45% (9/20) of patients, stage III in 5% (1/20) of patients and stage IV in 10% (2/20) of patients. The main type of endometriotic lesion in the adolescent was an atypical red vascular lesion, which was present in 60% (12/20) of adolescents; but it was present in only 20% (29/143) of non-adolescents. There were no intra-operative complications. Minor postoperative complications included one case of urinary tract infection and one case of port infection. The operative complications that developed when treating the non-adolescent group are presented for comparison. Pain scores recorded at follow-up revealed a significant reduction in dysmenorrhoea and pelvic pain and there was a positive effect on the quality of life of adolescents as measured by the EQ-5D questionnaire tool.	Adolescents with endometriosis use significantly more pain relief than non-adolescents to control symptoms. They have a higher rate of a first degree relative with the disease and they present with more atypical endometriotic lesions when compared with an adult population with endometriosis. All the stages of disease are present in the adolescent, including stages III and IV. The laparoscopic excision of endometriosis has a positive effect on the relief of pain symptoms and on the improvement in quality of life in the adolescent.	very small number of adolescents (20)
(Lee, *et al.*, 2017)	multicenter retrospective cohort study.	150 patients surgically treated with laparoscopic enucleation of endometriotic cysts younger than 20 years of age were selected. SETTING: Three university hospitals.	laparoscopic cyst enucleation	Endometrioma recurrence was considered when transvaginal or transrectal sonography indicated a cystic mass with a diameter of 20 mm or greater. Recurrence rate of endometrioma and median time to recurrence were evaluated.	In total, 105 patients were followed for 47.3 (+/-44.3) months (range, 3-161 months). Seventeen patients (16.2%) experienced recurrence after the first-line surgery and 8 patients (7%) underwent a second surgery. The median time to recurrence was 53.0 (+/-8.5) months (range, 8-111 months). Using Kaplan-Meier method, the cumulative recurrence rates of endometrioma per patient at 24, 36, 60, and 96 months after the first-line surgery were 6.4%, 10%, 19.9% and 30.9%, respectively. Surgical characteristics, such as the diameter of the cyst, revised American Society for Reproductive Medicine stage, unilateral or bilateral involvement, and coexistence of deep	Although the short-term recurrence rate in adolescents after first-line surgery is relatively low, the recurrence rate appears to be higher according to the follow-up duration. Long-term and continuous follow-up is needed for patients who have undergone surgical treatment for endometriosis in the adolescent period.	recurrence rate after cyst enuclaeation relatively low: enucleation effectiove surgical treatment option

					endometriosis were not associated with recurrence in this age group.		
(Tandoi, *et al.*, 2011)	Retrospective cohort study.	57 women aged </= 21 (mean age at diagnosis +/- SD: 19.0 +/- 1.1 years) undergoing first-line conservative surgery for endometriosis SETTING: University tertiary care referral center for women with benign gynecologic diseases. Data on age at surgery, disease stage, anatomical characteristics of endometriotic lesions, and endometriosis-related symptoms were collected.	After diagnosis, patients were treated according to the standard care of the center. The protocol required all women to be followed up 1 month after surgery, and every 6 months afterward, with an interview to investigate persistence of symptoms, a clinical examination, and an ultrasound pelvic assessment.	persistence of symptoms disease	During a 5-year follow-up, 32 (56%, 95% CI: 43%-68%) recurrences of endometriosis were diagnosed. A second laparoscopy to treat the recurrence was performed in 11 (34%) cases and confirmed the presence of the disease in all of them. In the remaining 21 (66%) cases, the recurrence was based on the reappearance of the symptoms or clinical or sonographic findings. The recurrence rate increased constantly with time from first surgery. No association emerged between recurrence rate and endometriosis-related symptoms, site/stage of the disease, type of surgery, and post-surgical medical treatment	The recurrence rate of endometriosis in young women appears higher than in older women. Since no determinants for recurrence have been detected among the factors examined, a profile of women at increased risk cannot be drawn.	

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	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, 2010a, Tandoi, *et al.*, 2011, Yeung, *et al.*, 2011). The studies summarized 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. Quality of evidence; ⊕◯◯◯
Balance between desirable and undesirable outcomes	Desirable outcomes: effective surgical treatment of pain Undesirable outcomes: complications of surgery; recurrence
Balance between different outcomes	Risk of complications of surgery does not always outweigh the relative benefit of surgical treatment, especially because recurrence rates may be considerable. To minimize complications and recurrence, a GPP on surgery for endometriosis in adolescents was added.
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	Surgery is expensive, but it is highly accepted by patients and doctors
RECOMMENDATION	**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.**

GPP	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.

Combined medical and surgical treatment

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Seo, *et al.*, 2017)	Cohort study	This study included 176 reproductive-aged women who underwent conservative laparoscopic surgery for pathology-confirmed endometrioma. Women were classified into 2 groups according to age: adolescents (20 years of age and younger, n = 34; group I) and reproductive-aged women (aged 25-35 years, n = 142; group II).	surgical removal of endometriosis, treatment with GnRH a and COC	Endometrioma recurrence was determined using ultrasonography.	During the treatment period (median, 41.0 months; range, 6-159 months), recurrence was noted in 8 cases (4.5%). After adjusting for confounders (which were statistically different between the groups), the cumulative proportion of recurrent endometriomas after 60 months was comparable between the 2 groups (5.3% in group I and 8.5% in group II).	Long-term postoperative medical treatment with cyclic oral contraceptives after a gonadotropin-releasing hormone agonist can be as effective in adolescents as it is in adults in the prevention of endometrioma recurrence.	
(Doyle, *et al.*, 2009)	Cohort study	Two academic medical centers. Sequential cases of young women identified on chart review with chronic pelvic pain unresponsive to dysmenorrheal treatment	initial laparoscopy for diagnosis and surgical destruction of endometriosis. All patients were then treated with standard continuous medical therapy (COC, P and/or GnRH analogue + add back). Patients with exacerbation of pain on anti-endometriosis medical	Endometriosis stage and adhesions at subsequent laparoscopy as compared to the initial surgical procedure.	90 patients met inclusion criteria. Eligible patients were 12 to 24 years of age at the time of the initial laparoscopy. The median endometriosis stage at first and second laparoscopy was I. No stage change was observed in 70% of patients, 19% improved by one stage, 1% improved by two stages, and 10% worsened by one stage. Regardless of initial	Based on the concept that endometriosis can be progressive, these data suggest that combined surgical-medical management retards disease progression in adolescents and young adults.	

			therapy who elected a subsequent laparoscopic procedure were eligible for this study.		stage, a trend toward disease progression was not observed. There was a significant likelihood for stage improvement at second laparoscopy, with those initially diagnosed as stage II or III most likely to exhibit improvement.		

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	Two low quality retrospective studies (Doyle et la., 2009; Seo et al., 2017) showing post-op treatment may retard progression/suppress recurrence Quality of evidence: ⊕◯◯◯
Balance between desirable and undesirable outcomes	Desirable outcomes: effective surgical and medical treatment of pain Undesirable outcomes: complications of surgery, recurrence, side effects of medication
Balance between different outcomes	Risk of complications of surgery does not always outweigh the relative benefit of surgical treatment, especially because recurrence rates may be considerable even if surgical treatment is combined with medical treatment
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	Combination of surgical and medical treatment is expensive, but it is highly accepted by patients and doctors, and in line with management in adults.
RECOMMENDATION	**In adolescents with endometriosis, clinicians should consider postoperative hormone therapy, as this may suppress recurrence of symptoms.**

QUESTION V.3 IS ENDOMETRIOSIS IN ADOLESCENTS AN INDICATION FOR FERTILITY PRESERVATION (OVARIAN TISSUE / OOCYTES)?

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Somigliana, *et al.*, 2015)	opinion paper	n/d	n/d	n/d	n/d	Personalized counseling should be offered to all patients with endometriosis taking into account age, extent of ovarian involvement, current ovarian reserve, previous and impending surgeries for endometriosis, along with current success rates and possible risks associated with FPT.	
(Carrillo, *et al.*, 2016)	opinion paper	n/d	n/d	n/d	n/d	women with endometriosis may represent a particularly suitable group since they are at increased risk of premature ovarian exhaustion and about half of them will experience infertility. Based on the currently available notions on the intricate relationships between endometriosis, infertility and damage to the ovarian reserve, we speculate that fertility preservation may be of interest for women with endometriosis, in particular for those with bilateral unoperated endometriomas and for those who previously had excision of unilateral endometriomas and require surgery for a contralateral recurrence. Young age at diagnosis may be an independent but pivotal additional factor to be taken into consideration in the balance of the pros and cons of fertility preservation. On the other hand, we argue against the introduction of fertility preservation for endometriosis in routine clinical practice. To date, only few cases have been reported and there are insufficient data for robust cost-utility analyses. It is noteworthy that endometriosis is a relatively common disease and systematically including affected women in a fertility preservation program would have profound clinical, logistic and financial effects. More clinical data and in-depth economic analysis are imperative prior to recommending its routine use.	

INCLUDED AS BACKGROUND INFORMATION
(Cobo, *et al.*, 2020)

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	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. 2 opinion papers were included which concluded that there is no evidence but fertility preservation may be considered Quality of evidence: NA
Balance between desirable and undesirable outcomes	Desirable outcome: chance to remain fertile despite endometriosis Undesirable outcome: ovarian damage or increase of endometriosis symptoms due to procedure / unrequired additional procedure (no effect of fertility preservation on fertility chance)
Balance between different outcomes	High success rates of fertility preservation may outweigh the risks in selected patients, however question is whether (and in whom) fertility preservation is really necessary to protect fertility.

	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.
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	Fertility preservation is expensive and offering this in all adolescents with endometriosis in routine clinical practice would have large clinical, logistic and financial effects. To date, cost-utility analyses are lacking
GPP	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.

QUESTION VI.1 IS ENDOMETRIOSIS STILL ACTIVE DURING MENOPAUSE AND IF SO, HOW SHOULD THE SYMPTOMS BE TREATED?

NARRATIVE QUESTION

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Not applicable

INCLUDED REFERENCES (Narrative question)
(Bendon and Becker, 2012, Henriksen, 1955, Matalliotakis*, et al.*, 2019, Oxholm*, et al.*, 2007, Polyzos*, et al.*, 2011, Punnonen*, et al.*, 1980, Ranney, 1971, Streuli*, et al.*, 2017) (Attar and Bulun, 2006, Gemmell*, et al.*, 2017, Noble*, et al.*, 1996)

EVIDENCE TO RECOMMENDATIONS

Not applicable

The GDG formulated the following conclusion:

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

QUESTION VI.2 IS SURGICAL/MEDICAL TREATMENT EFFECTIVE AND SAFE IN WOMEN WITH A HISTORY OF ENDOMETRIOSIS?

Surgical treatment

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Redwine, 1994)	prospective, longitudinal observational study	75 patients with previous castration had biopsy-proven endometriosis excised surgically. Control group: non-castrated women with endometriosis. Patients were significantly older (37.8 +/- 8.1 versus 31.3 +/- 6.9 years)	Surgical excision	Anatomical characteristics of disease Preoperative and postoperative verbal analogue pain scales	Patients were slightly more likely to have intestinal involvement (risk ratio 1.3, 95% CI 0.94-1.8) than controls. Most patients had marked alleviation of pain after excision of endometriosis. No malignancy was found in this study	Endometriosis can remain symptomatic after castration, with or without estrogen therapy. In such patients, there is a 33% frequency of intestinal involvement. At castration, consideration should be given to removal of invasive peritoneal and intestinal disease. Symptom improvement occurs in most patients after excision of endometriosis.	
(Behera, *et al.*, 2006)	Retrospective cohort	124 patients with chronic pelvic pain after hysterectomy and BSO	laparoscopic and histopathologic evaluation of the pelvis. Diagnostic + CO2 laser resection	Laparoscopic and histopathologic findings of the pelvis, as well as subjective pain improvement	The most common histopathologic findings included adhesions (in 94% of patients), adnexal remnants (26%), and endometriosis (15%)in 23%. Laparoscopic treatment of any pelvic pathologic condition improved pain symptoms in the majority of these women (58.9%). In 2 women (1.4%) a malignancy of the bowel was found.	The most common histopathologic findings at laparoscopy in women with chronic pelvic pain after Hx and BSO included adhesions, adnexal remnants, and endometriosis. Laparoscopic treatment improved pain symptoms	
(Clayton, *et al.*, 1999)	case series	5 women with recurrent pain after BSO and hysterectomy who had residual endometriosis	laparoscopic excision of residual endometriosis	Immunoreactivity for estrogen, progesterone receptor Pain relief	Four of the women had bowel endometriosis. Immunohistochemistry showed positive immunoreactivity for estrogen and progesterone receptors in all patients, suggesting that the endometriosis was highly active and responsive to exogenous estrogen.		

					All women had improved pain symptoms.		
(Morotti, *et al.*, 2012)	retrospective cohort study	72 postmenopausal women with endometriosis. median age of patients at the time of surgery was 58.5 years. Eleven patients (15.3%) had previous history of endometriosis and 5 patients had previous surgery for this reason. 2 patients were using HRT at the time of surgery. :	surgery	the preferential location, extension and histopathological features of the lesions.	The most frequent location of endometriotic lesions was the ovary and among patients with endometriomas, 35% (20/57) had different grades of metaplasia, hyperplasia, atypia and endometrioid carcinoma arising in endometriosis. The proportions of epithelium, stroma and hemorrhage in endometriotic lesions were higher in patients with concomitant endometrial or ovarian cancer.	Endometriosis should be considered in the differential diagnosis of postmenopausal cystic lesions of the ovary. The administration of exogenous estrogen is not a prerequisite for the presence of endometriosis in postmenopausal women	
(Sun, *et al.*, 2013)	retrospective cohort	69 patients ranged from 47 to 80 ((56.5±6.4) years). They had been postmenopausal for 2 to 29 years, with an average of (5.9±5.5) years. The average BMI of these patients was 27.3±4.4, ranging from 18.8 to 41.7. Of the 69 women, 45 (65%) were referred with an abdominal mass without symptoms, only 8 women presented with abdominal pain.	Surgery + histology		In 62 women an endometrioma was found and 10 women (14%) had a coexisting ovarian, endometrial or cervical malignancy.		

INCLUDED AS BACKGROUND INFORMATION
(Oxholm, *et al.*, 2007, Pavone and Bulun, 2012, Polyzos, *et al.*, 2011)

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	The evidence available from cohort studies show that surgical treatment can improve pain in postmenopausal women with endometriosis. In women with endometriosis, and specifically endometrioma, there seems to be a significant proportion with concordant malignancy. Quality of evidence: ⊕◯◯◯
Balance between desirable and undesirable outcomes	Benefit of surgery: diagnosing a possible malignancy and treatment of pain symptoms Risks: recurrence of symptoms; risk of (underlying) malignancy; risk of possible complications from surgery

Balance between different outcomes	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 confirm the diagnosis of endometriosis seem to outweigh the possible complications of surgery. In addition, surgery may have a benefit towards excluding malignancy and/or reducing the risk of future malignancy
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	Surgery is feasible in most women, however one should keep in mind the possible risks of complications
RECOMMENDATION	**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.**
GPP	**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.**

Medical treatment

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Polyzos, *et al.*, 2011)	Review	5 case reports Patients' age ranged from 47 to 61 years old. The majority of them had total abdominal Hx and BSO at earlier age. 2 patients had received HRT during menopause, one until recurrence of endometriosis and one more than 3 years prior recurrence. The majority of women had been previously treated for endometriosis with either surgery, or GnRH agonists or progestins. 4 surgical, 1 natural menopause	letrozole or anastrozole	Efficacy for endometriosis related pain endometriotic lesions size	In all treated patients, administration of letrozole or anastrozole appeared to improve pain related to endometriosis, either when treatment was administered for 4 months or for up to 15 months. Furthermore, letrozole appeared to improve all the other symptoms, such as urinary tract and bowel symptoms, whenever these systems were affected by endometriosis. Nonetheless, exemestane did not improve endometriosis symptoms in one patient, who later showed relief of symptoms with letrozole In all of the patients in which clinical manifestation of the disease was the presence of endometriotic masses, AIs significantly reduced the size of the lesions as measured by imaging		

(Pavone and Bulun, 2012)	Review	All patients had undergone either surgical or natural menopause, with several patients having been exposed to HRT. Most women were previously treated for endometriosis with either surgery, GnRH agonists, or progestins.	letrozole or anastrazole for 4–18 months	Efficacy (pain, lesion size) Side effects	improved endometriosis related pain. Subjective symptoms decreased and endometriotic lesion size (by physical exam findings or imaging), were also reduced. Only one patient reported hot flushes. Co-administration of bisphosphonates was given in two patients and one reported letrozole associated bone loss, with a slight reduction of BMD after 9 months of anastrazole treatment	Included the same case reports as Polyzos 2011, with addition of Razzi 2004.	

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	Based on the biological aspects, AIs are probably the most appropriate medical treatment for endometriosis-related pain symptoms in postmenopausal women. Although evidence is limited to case reports in postmenopausal women, the efficacy of AIs can be deduced from studies in premenopausal women. Quality of evidence ; ⊕◯◯◯ (case reports)
Balance between desirable and undesirable outcomes	Benefit: treatment of pain symptoms and improving QOL. Risks: recurrence of symptoms; risk of (underlying) malignancy; risk of possible side effects from medical treatment
Balance between different outcomes	Evidence of benefit is limited, and surgery seems to be a more established treatment option. Still, Ais could be considered a treatment option, for instance when surgery is not feasible, contra-indicated, or when surgery was insufficient to resolve symptoms
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	Treatment with AIs is feasible, however no evidence except for case reports exists.
RECOMMENDATION	**For postmenopausal women with endometriosis-associated pain, clinicians may consider aromatase inhibitors as a treatment option especially if surgery is not feasible.**

QUESTION VI.3 IS HORMONE TREATMENT EFFECTIVE AND SAFE FOR RELIEF OF MENOPAUSAL SYMPTOMS IN WOMEN WITH A HISTORY OF ENDOMETRIOSIS?

No intervention compared to HRT – natural menopause

No studies

INCLUDED AS BACKGROUND INFORMATION
(Baber, *et al.*, 2016); (The ESHRE Guideline Group on POI, *et al.*, 2016).

No intervention compared to HRT – surgical menopause

Summary of Findings Table

No intervention compared to HRT for menopausal symptoms in postmenopausal endometriosis

Patient or population: postmenopausal endometriosis
Intervention: no intervention
Comparison: HRT

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with HRT	Risk with no intervention				
Recurrence assessed with: histological confirmation, or by clinical findings (pelvic pain and/or pelvic mass)	35 per 1,000	**157 per 1,000** (9 to 1,000)	**RR 4.50** (0.25 to 82.17)	172 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	Matorras et al. (2002) in Gemmell et al. (2017)
Recurrence	44 per 1,000	**79 per 1,000** (4 to 1,000)	**RR 1.78** (0.10 to 31.64)	107 (1 observational study)	⨁◯◯◯ VERY LOW [b,c]	Rattanachaiyanont et al. (2003) in Gemmell et al. (2017)
Recurrence	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	19 (1 observational study)	⨁◯◯◯ VERY LOW [b,d]	Acien et al. (2013) in Gemmell et al. (2017)

Explanations
a. High risk of performance bias—single blinded study, with physician unaware of treatment allocation, but with access to hormone results (which would have indicated treatment with HRT or not). High risk of detection bias, as assessment for recurrence was only carried out if the clinician felt this was warranted, which may have been influenced by the participant (who was not blind to treatment allocation).
b. Single study - Very wide CI for RR.

c. High risk of selection bias as unclear why women were allocated to different HRT regimens (or no HRT). High risk of detection bias, as researchers would have been aware of the woman's HRT status when assessing presence of recur- rence (by reviewing medical records).
d. Risk of detection bias, as criteria for designating recurrence are not clearly stated.

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Gemmell, *et al.*, 2017)	3	CASE REPORTS + SERIES 42 patients Age range (years) (mean (years)) 30–75 (52) Type of menopause • Surgical: 36 • Natural: 4 Presumed natural + oophorectomy later: 2	HRT Mean duration of HRT (years): 7.8 Unopposed oestrogen (n): 31		Endometriosis recurrence (n): 17 Malignant transformation (n): 25 Mortality (n): 3		
		Observational studies and clinical trials (6 studies)		Recurrence	(See SOF TABLE)	Given the concerns of possible disease reactivation or malignant transformation of endometriotic foci, it is reasonable to consider whether treatment with HRT is justifiable in this group of women. However, in a field dominated by case reports and series, it is challenging to obtain information on risk.	
(Matorras, *et al.*, 2002)	RCT	Included in review Gemmell et al. (2017)					

HRT compared to Tibolone

Summary of Findings Table

HRT compared to Tibolone for menopausal symptoms in postmenopausal endometriosis

Patient or population: postmenopausal endometriosis
Intervention: HRT
Comparison: Tibolone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Tibolone	Risk with HRT				
Recurrence	91 per 1,000	**400 per 1,000** (54 to 1,000)	**RR 4.40** (0.59 to 33.07)	21 (1 observational study)	⊕◯◯◯ VERY LOW [a,b]	Fedele et al. (1999) in Gemmell et al. (2017)

Explanations
a. High risk of selection bias (unclear why some women started HRT after 3 months and some after 5 months), and high risk of detection bias (recurrence was only based on CA 125 levels).
b. Very wide CI for RR.

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Fedele, *et al.*, 1999)	RCT	Included in review Gemmell et al. (2017) – SOF TABLE					
(Sundar, *et al.*, 2007)	Case report	52 year old women	hysterectomy with ovarian conservation 2.5 mg of Tibolone for menopausal symptoms	recurrence	Four months after commencing the hormone replacement therapy, vaginal examination revealed a mass at the vaginal vault, which was confirmed on computerised tomography. Due to the unusual nature of presentation and the suspicion of malignancy, a laparotomy was performed, which showed a 565 cm mass densely adherent to the external iliac vein and ureter, extending into the obturator fossa. The mass was excised with difficulty with injury and repair of the external iliac vein. An infracolic omentectomy was performed as the omentum was infiltrated with multiple small nodules. Surprisingly, histology revealed an endometrioma similar to previous ovarian histology with active endometriosis in the omental nodules		Included in review Gemmell et al. (2017)
(Chen, *et al.*, 2019)	Systematic Review	Menopausal Women 95 abstracts and 68 full-text articles	Isoflavone Supplements (focusing on the active ingredients daidzein, genistein, and S-equol)	hot flashes BMD BP glycemic control	isoflavones - reduce hot flashes (even accounting for placebo effect), - attenuate lumbar spine BMD loss, - show beneficial effects on systolic blood pressure during early menopause, - improve glycemic control in vitro. There are currently no conclusive benefits on urogenital symptoms and cognition.	evidence thus far favors the use of isoflavones due to their safety profile and benefit to overall health	

(Løkkegaard and Mørch, 2018)	Danish Sex Hormone Register Study i	988,524 peri- or post-menopausal women with no previous cancer (except non-melanoma skin cancer) or bilateral oophorectomy accumulated 9.0 million person-years; corresponding to an average follow-up of 9.8 years. A total of 914,595 had no previous cancer or hysterectomy. The number of incident malignant ovarian cancers during the study period was 4,513. Of these, 2,221 were serous ovarian cancer 454 endometrioid, 388 mucinous and 206 clear cell tumors. The number of endometrial cancers was 6,202 of which 4,972 were Type I endometrial cancers and 500 Type II tumors. At the end of follow-up 64% of the women had not been taking HT, 17% were previous users of systemic hormones, 0.4% were current users of tibolone, 8% were current users of systemic hormones other than tibolone and 11% were ever users of local hormones.	Tibolone	Risk of cancer	Compared to women never on postmenopausal hormone therapy, current users of tibolone had an increased IRR for ovarian cancer (1.42(95% confidence interval [CI], 1.01-2.00) and serous ovarian tumors (2.21(95%CI 1.48-3.32)). IRR of endometrial cancer was 3.56 (95%CI 2.94-4.32) among current users of tibolone and 3.80 (95%CI 3.08-4.69) of Type I endometrial cancer.	t use of estrogen alone, tibolone and sequential combined therapy increases risk of cancer, even when treatment lasts less than 5 years. Continuous combined therapy might present a lower risk than never use, and therapy for more than 10 years does not increase risk. Micronized progesterone increases the risk of endometrial cancer regardless of regimen.	

INCLUDED AS BACKGROUND INFORMATION
(Al Kadri*, et al.*, 2009, North American Menopause Society, 2011)

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	Evidence from observational studies and 2 small RCTs is summarized in Gemell 2017. Direct evidence is only available for women with surgical menopause (low quality) Very low quality, scarce indirect evidence (recurrence of symptoms/risk of malignancy) Efficacy of HRT for treatment of menopausal symptoms is considered established based on indirect data from general population. The impact of HRT on recurrence of endometriosis (2 small RCTs, 4 observational studies and 33 case reports) was recently summarized in a systematic review, showing a possibly increased risk. Incidence of malignancy: very few cases have been reported for estrogen combined with progestogens. Quality of evidence : ⊕⊕◯◯
Balance between desirable and undesirable outcomes	Benefit: treatment of climacteric and genitourinary symptoms, prevention of bone loss and improving QOL. Risks: recurrence of symptoms; risk of malignancy

Balance between different outcomes	With very low incidence of recurrent endometriosis after menopause and even lower risk of malignancy, the benefits seem to outweigh the risks in women with climacteric symptoms. 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. Tibolone is associated with a higher risk of endometrial carcinoma than continuous combined therapy and hence not included in the recommendation.
Patient values and preference	*No data*
Resource use, equity, acceptability and feasibility	Hormonal treatment is feasible, costs are quite low, treatment is acceptable.
RECOMMENDATION	**Clinicians may consider combined HRT for the treatment of postmenopausal symptoms in women (both after natural and surgical menopause) with a history of endometriosis.**
RECOMMENDATION	**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**
GPP	**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.**

Phytoestrogens

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Noel*, et al.*, 2006)	Case report		5-year use of a highly concentrated isoflavone supplement		florid recurrence of endometriosis and ureteral malignant mullerian carcinosarcoma		

INCLUDED AS BACKGROUND INFORMATION
(Cotroneo and Lamartiniere, 2001); (Tsuchiya*, et al.*, 2007, Yavuz*, et al.*, 2007)

EVIDENCE TO RECOMMENDATIONS

No recommendations (insufficient data to support a recommendation)

QUESTION VI.4 ARE WOMEN WITH ENDOMETRIOSIS AT HIGHER RISK OF EXPERIENCING MENOPAUSE-RELATED MAJOR HEALTH CONCERNS?

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Not applicable

INCLUDED REFERENCES (Narrative question)
(Farmer, *et al.*, 2003, Georgakis, *et al.*, 2019, Mu, *et al.*, 2017, Mu, *et al.*, 2016, Shigesi, *et al.*, 2019)

EVIDENCE TO RECOMMENDATIONS

Not applicable

The GDG formulated the following 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

QUESTION VII.1 HOW RELIABLE IS IMAGING FOR DIAGNOSING EXTRAPELVIC ENDOMETRIOSIS?

Abdominal wall, umbilical, perineal and inguinal endometriosis

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Andres, *et al.*, 2020)	Systematic review of 179 articles, mostly case reports and series	Abdominal Endometriosis-Parietal Endometriosis		Presentation (88 studies; 230 patients) Imanging (86 studies, 120 patients)	133 were in the groin, 82 were umbilical, 13 were in the abdominal wall, and 2 were in the perineum. All cases were primary lesions, that is, patients did not have any previous abdominal and perineal surgery or vaginal deliveries. Associated pelvic endometriosis was evaluated for in a total of 134 patients with PE and was found in 18% (25/134) of patients Median age of patients at presentation was 38.5 (range, 25–73) years. Most common clinical presentations: palpable mass (99%; 221/223), cyclic parietal pain (71%; 76/107), umbilical bleeding (48%; 38/ 78), and acyclic parietal pain (32%; 32/110). US was the most common (41%; 50/120) imaging modality used to diagnose PE, followed by MRI (18%; 22/120) and CT (12%; 15/120;		*Data on other extrapelvic endometriosis subtypes/diagnosis /treatment are included in the respective evidence tables*
(Andres, *et al.*, 2020)	Systematic review of 179 articles, mostly case reports and series	Abdominal Endometriosis-Visceral Endometriosis		Presentation (43 patients) ^ Imaging	28 liver, 10 kidney, 3 pancreas, and 2 biliary tract median age : 40.3 (range, 25–73) yrs Symptoms : upper abdominal pain (77%; 21/27) and abdominal mass (11%; 11/27) in patients with liver endometriosis; flank pain (60%; 6/10), hematuria (20%; 2/10), and pyelonephritis (20%; 2/10) in patients with kidney endometriosis; epigastric pain (100%; 3/3) and acute pancreatitis (33%; 1/3) in patients with pancreatic endometriosis; and acute liver failure (50%; 1/2) and upper abdominal pain (50%; 1/2) in patients with liver endometriosis. The most commonly used imaging modality for patients with VE was CT (72%; 31/43). I		
(Chamie, *et al.*, 2018)	review		Abdominal wall: Various imaging modalities can be used for diagnosis of abdominal wall endometriosis, including color Doppler US, CT, and MR imaging. Umbilicus: R imaging has been shown to be the best choice for diagnosis and is very useful to define the size, extension, and hemorrhagic content of cysts.	**Abdominal wall:** performed with a linear transducer will demonstrate a hypoechoic nodule or mass with irregular contours, sometimes containing small cystic areas with or without thick content and small scattered hyperechoic echoes. At color Doppler US, a hypovascular pattern with small peripheral vessels is seen. US is the most cost-effective imaging modality and should be performed first. At CT, an endometriotic nodule appears as a circumscribed solid mass that enhances with contrast agent administration. MRI is more accurate for diagnosis, especially when small hemorrhagic areas are present within the nodule, which increases the specificity for diagnosis. The excellent spatial and contrast resolution of the method allow better tissue definition, which is valuable in defining the extent of disease, the integrity of the surrounding muscle tissue, and other affected structures. Endometriotic lesions typically have low signal intensity on T2-weighted images, with high-signal-intensity small cystic areas and spiculated margins. On T1-weighted images, they demonstrate intermediate signal intensity with hemorrhagic internal areas of high signal intensity and contrast enhancement.	Extrapelvic endometriosis is rare and can be difficult to diagnose because of the great variability in location and clinical manifestations.	

				Umbilicus: The typical MR imaging finding is a nodule with low signal intensity on T2-weighted images, intermediate signal intensity on T1-weighted images, internal cystic areas with high signal intensity on fat-saturated T1-weighted gradient-echo images, and enhancement after contrast material injection. Inguinal area: or Doppler US will demonstrate a hypoechoic mass with absent flow, with or without cystic areas. The cystic portion is usually filled with thick fluid and has a ground-glass appearance. MRI is more accurate than US because it can demonstrate the old hemorrhagic content of the cyst. **Thoracic cavity:** chest radiography and thin-section CT may reveal pneumothorax, pleural effusions, nodules, opacities and nodular infiltrates, thin-walled cavities, segmental atelectasis, and bullous formation. MRI patterns include lesions that vary from punctate spots to large nodules, or confluent plaques with low signal intensity on T2-weighted images and high signal intensity on T1-weighted gradient-echo images due to the hemorrhagic content. Cystic areas and contrast enhancement are also common findings.			
(Yarmish, *et al.*, 2017)	retrospective	only cases with CT studies performed within 12 months prior to histopathologic evaluation were considered, yielding a cohort of 111 cases. Of these, 5 cases were excluded because the biopsied mass was along the pelvic sidewall and 1 case was excluded because the biopsied mass was in the left upper quadrant and not within the anterior abdominal or pelvic wall soft tissues. The final cohort included 105 patients with median age 41 years (range: 21-55 years); 24.8% (26/105) had histologically proven endometriosis.	CT scans were performed on 16 or 64 detector row GE helical scanners Images were reconstructed at 2.5-mm or 5-mm intervals. Iodinated intravenous contrast material (120 – 150 cm Omnipaque-300) was administered to 76 of 105 patients (72.4%)	endometriosis patients had a higher proportion of homogeneous density masses (R1: 88.5% vs. 58.2% and R2: 88.5% vs. 57%), and masses located below the umbilicus compared with other patients (R1: 96.2% vs. 70.9% and R2: 96.2% vs. 69.6%	endometriosis patients had a higher proportion of homogeneous density masses (R1: 88.5% vs. 58.2% and R2: 88.5% vs. 57%), and masses located below the umbilicus compared with other patients (R1: 96.2% vs. 70.9% and R2: 96.2% vs. 69.6%	Significant differences were observed; the presence of "gorgon" sign, mass homogeneity and location below the umbilicus were significantly associated with endometriosis. We defined the "gorgon" sign as the presence of linear infiltration radiating peripherally to the adjacent subcutaneous fat from a central soft tissue nodule.	
(Gidwaney, *et al.*, 2012)	review		UltrasonographyUS is usually the first imaging examination performed to evaluate focal abdominal or pelvic wall thickening identified at clinical examination, and it may be performed in patients with focal abdomi-nal or pelvic pain that is localized to a surgical scar with no identifiable abnormality at physical examination. T may be performed with or without intravenous contrast material, although the use of contrast material improves its sensitivity and specificity.MR imaging provides better contrast resolution than CT and US and is superior to CT for depicting the delineation between muscles and abdominal subcutaneous tissues and infiltration of abdominal and pelvic wall structures		With US, scar endometriosis may demonstrate irregular, often spiculated, margins, with infiltration of the adjacent soft tissues. If gray-scale, color, and power Doppler US findings are inconclusive, the extent and biologic behavior of the lesion may be further evaluated at MR imaging. At pelvic CT, an area of concomitant central low attenuation may be seen within the uterus, a finding consistent with menstruation. Scar endometriosis may be isointense relative to muscle on T1-weighted images.	In a woman with an abdominal or pelvic anterior wall mass or an area of soft-tissue thickening at cross-sectional imaging in the location of a previous surgical scar, endometriosis should be strongly considered by the interpreting radiolo-gist. CT, US, and, particularly, MR imaging may help establish a diagnosis of scar endometriosis.	

(Hirata, *et al.*, 2020)	retrospective national survey Obstetrics and Gynecology and Plastic Surgery Departments at a teaching hospital in Japan.	Patients with umbilical endometriosis or malignant transformation. A national survey was conducted to identify and evaluate cases of umbilical endometriosis or malignant transformation documented between 2006 and 2016. 96 patients were identified with pathologically diagnosed benign umbilical endometriosis.	age at diagnosis, body mass index, medical history, presence of extragenital endometriosis, surgical history, symptoms, imaging modalities, surgical therapy, hormonal therapy, follow-up period, postoperative recurrence, and time to recurrence.	Symptoms Sensitivity	The patients frequently had swelling (86.5%), pain (81.3%), or bleeding (44.8%) in the umbilicus. Sensitivity was 87.1% for physical examination, 76.5% for transabdominal ultrasonography, 75.6% for computed tomography, and 81.8% for magnetic resonance imaging.		DIAGNOSIS DATA
(Horton, *et al.*, 2008)	systematic review of published cohorts	29 articles describing 455 patients pooled mean age: 31.4 years. 96% presented with a mass, 87% presented with pain, and 57% with cyclic symptoms.	Clinical presentation Treatment	Diganosis Recurrence	Abdominal wall endometriosis (AWE) was associated with a caesarian scar or hysterectomy in 57% and 11% of cases, respectively. The interval from index surgery to presentation was 3.6 years. Recurrence after resection was 4.3%. The most common presentation of AWE is the development of a painful mass after uterine surgery. Surgical treatment appears to result in a cure more than 95% of the time.		

Thoracic endometriosis

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Johnson, 2004)	(narrative) review	thoracic endometriosis syndrome		Manifestations of thoracic endometriosis syndrome Discussion of different options for diagnosis through US	Pneumothorax Hemothorax Hemoptysis Chest pain Dyspnea Pulmonary nodules Pleural mass Pleural effusion Pneumomediastinum Vascular invasion		
(Rousset, *et al.*, 2014)	review	thoracic endometriosis syndrome	The CT images shown in this review were acquiredon a 16-detector-row device with the following parameters: 160.75 mmcollimation, 0.75 s rotation time, pitch 1, 90 or 120 kVdepending on patient weight and the indication, automaticexposure control by	Diagnostic value	Although the CT aspect of TES is poorly specific, CT re-mains thefirst-line imaging method, as it can rule out other diagnoses and map the lesions for surgery if necessary. MRI is an interesting imaging tool for confirming thoracic endometriosis. The lack of spatial resolution (compared to CT) is compensated for by high contrast resolution and	Diagnosis of TES is challenging, as these women's symptoms may not immediately be attributed to endome-triosis, and as some radiological abnormalities (especially pneumothorax and haemoptysis) are non-specific or maybe taken for	

			DoseRight Dynamic Dose Modulation(D-DOM), and a standard reconstruction algorithm (1 mmsection reconstruction thickness with 30% overlap). The MR images shown in this review were acquired on a 1.5 T MRI (Achieva, Philips Medical Systems, Best, The Netherlands). MRI examinations are based on morphological sequences acquired during breath-holds, and include fast spin-echo T2 with or without fat saturation, unenhanced T1, and t3D gradient-echo T1 with fat saturation (eTHRIVE) weighted sequences, each performed in the axial and coronal planes.		better characterization of haemorrhagic lesions.	artefacts (notably endometriotic diaphragmatic implants on MRI).	
(Andres, *et al.*, 2020)	Systematic review of 179 articles, mostly case reports and series	Thoracic endometriosis (34 case series; 628 patients) 11 studies (495 patients) reported on diaphragmatic endometriosis, 5 studies (90 patients) on pleural, and 21 studies (28 patients) on lung endometriosis.		Presentation TE (628 patients) Imaging TE	In 1.11% (7/628) of patients, concomitant diaphragmatic, pleural, and lung involvement. isolated lesions: diaphragm (44.5% (280/628)); pleura (12.7% (80/628)); lung (4.5% (28/628)) median age: 22.6 (range, 16–54) years. diagnosis was confirmed by histologic analysis preoperatively Pneumothorax was the most common presenting symptom (69.9%; 439/628) in TE cases. TE was right sided in 80% of cases. The mean number of episodes of pneumothorax was 3.1 ± 2.7. The association of TE and pelvic endometriosis was found in 52.9% (186/351) of women from 13 studies, The most common initial imaging examination used was chest X-ray (31%; 189/600) For diaprahgmatic endo : MRI has accuracy of 83%		*Data on other extrapelvic endometriosis subtypes/diagnosis/treatment are included in the respective evidence tables*
(Vigueras Smith, *et al.*, 2020)	Review	diaphragmatic endometriosis MEDLINE search			under-diagnosed disease affecting between 0.1% and 1.5% of fertile women. It is predominantly multiple, asymptomatic and highly associated with pelvic disease in about 50-90%.		

(Joseph and Sahn, 1996)	Review	A MEDLINE search All information given as individual case reports and small series were utilized for this study.		Clinical presentation	From 110 of the 112 identified cases, the following observations were made: age at the time of diagnosis, duration of symptoms before diagnosis, clinical presentation, hemithorax affected, relation to menstruation, presence of pelvic endometriosis, previous pelvic operations, pathological findings observed at thoracotomy or thoracoscopy, methods of treatment, and outcome. For estimating the age-specific incidence of TES, patients were divided into seven class intervals. The age-specific incidence of the present study was then compared with the age-specific incidence of pelvic endometriosis from an established study.		
(Gil and Tulandi, 2019)	SR	18 studies, with a total of 490 patients. The search was limited to trials in humans and published in English language in the past 20 years up to November 2018. The inclusion criteria were: clinical articles, case series with over 5 patients, cohort studies, reviews, and meta-analyses.	Diagnosis surgery and medical treatment presented (See VII.2)		Most of the publications were retrospective cohort studies, and 1 study was a prospective study. History should always include catamenial extrapelvic symptoms such as chest pains, dyspnea, or hemoptysis.	To achieve a better understanding and treatment of this condition, we propose creating a registry on thoracic endometriosis involving gynecologists,pneumologists , and thoracic surgeons.	

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	There is limited evidence on extrapelvic endometriosis. Published data include reports or retrospective cohort studies. 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.
Balance between desirable and undesirable outcomes	Diagnosis (and treatment) of extrapelvic endometriosis Harms include overdiagnosis, incorrect diagnosis and overtreatment
Balance between different outcomes	There is no evidence on the most appropriate diagnostic approach in extrapelvic endometriosis. Recommendations are limited to awareness of symptoms and referral to a centre with sufficient expertise
Patient values and preference	No data

Resource use, equity, acceptability and feasibility	Awareness and referral are feasible and acceptable actions.
GPP	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.

QUESTION VII.2 DOES TREATMENT FOR EXTRAPELVIC ENDOMETRIOSIS RELIEVE SYMPTOMS ?

Abdominal wall, umbilical, perineal and inguinal endometriosis

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Andres, *et al.*, 2020)	Systematic review of 179 articles, mostly case reports and series	Abdominal Endometriosis- Parietal Endometriosis	Surgical/medical treatment	Feasibility complications	Only 5 case reports of umbilical endometriosis described the use of preoperative medical treatment, Surgery was performed in 97% (222/227) of PE cases Complete excision of the PE lesion was accomplished in 99.3% (150/151) cases, and no studies reported on any postsurgical complications. 10 cases reported the use of adjuvant hormonal treatment after surgery Recurrences of lesions: in 5% (7/135) of cases.		*Data on other extrapelvic endometriosis subtypes/diagnosis/treatment are included in the respective evidence tables*
		Abdominal Endometriosis- Visceral Endometriosis	Surgical/medical treatment	Feasibility complications	Hormonal treatment only ; 7.6% (3/39) of VE cases. Surgery was performed in 86% (37/43) of cases; Conservative surgery procedures (in 51% (19/37)) included local resection (40%; 15/37), drainage (5.4%; 2/37), and partial nephrectomy (5.4%; 2/37), More radical procedure (n 49% (18/37)), included partial hepatectomy (3.0%; 11/37) and complete nephrectomy (10.8%; 4/37) Postsurgical complications : 1 death caused by liver failure 7 days after partial hepatectomy + 1 biliary leakage after hepatic cystectomy No treatment – 1 asymptomatic patient Of the 42 surgical cases: - no recurrence 38.0% (16/42) - recurrence : 15% (3/42) (all liver) - 54.7% (23/42) no information on recurrence		
(Hirata, *et al.*, 2020)	retrospective national survey	Patients with umbilical endometriosis or malignant	age at diagnosis, body mass index, medical history, presence of extragenital	recurrence rate	The cumulative recurrence rate was 1.34% at 6 months, 6.35% at 12 months, and 6.35% at 60 months after surgery. Importantly, there	There was a low recurrence rate following surgery, and	TREATMENT DATA

	Obstetrics and Gynecology and Plastic Surgery Departments at a teaching hospital in Japan.	transformation. A national survey was conducted to identify and evaluate cases of umbilical endometriosis or malignant transformation documented between 2006 and 2016. 96 patients were identified with pathologically diagnosed benign umbilical endometriosis.	endometriosis, surgical history, symptoms, imaging modalities, surgical therapy, hormonal therapy, follow-up period, postoperative recurrence, and time to recurrence.		was no recurrence after wide resection including of the peritoneum (0 of 37 cases). The efficacy of dienogest (an oral progestin), gonadotropinreleasing hormone agonists, and oral contraceptives was 91.7%, 81.8%, and 57.1%, respectively. Finally, 2 cases of malignant transformation were identified.	hormonal treatment is an option, although the current findings suggest surgical therapy as the first choice of treatment for umbilical endometriosis	
(Song, *et al.*, 2011).	Case report	A 45-year-old woman presented with lower abdominal pain 2 years following a laparoscopic supracervical hysterectomy. She was found to have incidental cholelithiasis and a large abdominal mass suggestive of a significant ventral hernia on CT scan.			Due to the peculiar presentation, surgical intervention took place that revealed a large 9cmx7.6cmx6.2cm abdominal wall endometrioma.	Although extrapelvic endometriosis is rare, it should be entertained in the differential diagnosis for the female patient who presents with an abdominal mass and pain and has a previous surgical history.	
(Nissotakis, *et al.*, 2010)	case report + literature review				Endometriosis is the presence of ectopic endometrial tissue that can respond to ovarian hormonal stimulation. Although it is uncommon, extrapelvic endometriosis can form a discrete mass known as an abdominal wall endometrioma. Endometriomas are thought to be caused by transfer of endometrial cells into a surgical wound, most often after a cesarean delivery. Endometriomas are diagnosed via ultrasound, computed tomography, magnetic resonance imaging, and ultrasound-guided fine needle aspiration. Treatment options can be medical, but surgical excision is the treatment of choice. Perioperative nursing care includes patient teaching, taking steps to prevent surgical site infection and inadvertent hypothermia, ensuring availability of supplies (eg, the graft for abdominal wall repair if needed), and postoperative pain management.		
(Marinis, *et al.*, 2006)	Case report (4 cases)	4 patients with extragenital endometriosis of the abdominal wall		clinical manifestations, the radiologic appearance treatment	In two patients endometriosis was found adherent with the structures of the inguinal canal and in the other two the tumors infiltrated structures of the abdominal wall. Symptoms included cyclical pain and palpable subcutaneous masses fixed to the surrounding tissues. CT – MRi failed to differentiate the lesions from other soft tissue tumors. Resection to healthy tissue margins is the treatment of choice, in order to avoid local recurrence.		
(Liang, *et al.*, 1996)	Case report (6 cases)	6 patients with perineal endometriosis perineal endometriosis	Management comprised both surgical and medical treatment. Postoperative	clinical symptoms and signs	clinical symptoms and signs which included cyclic perineal pain and a tender perineal mass coinciding with the menstrual cycle.	A detailed history, thorough pelvic examination and sonographic	

			follow-up was carried out at 3-monthly intervals.	Diagnosis Management	Diagnostic tools used included US, CT, fine needle aspiration cytology and laparoscopy. All six patients were cured following surgical excision of the endometrioma.	investigation are essential in diagnosing perineal endometriosis. The role of other diagnostic tools remains controversial. Treatment of extrapelvic endometriosis includes surgical intervention and hormonal suppression. If hormonal suppression fails, surgical excision of the perineal endometrioma should be carried out.	
(Horton, *et al.*, 2008)	SR	An English language PubMed search was conducted for every case report, series, and literature review relating to AWE. Key words used were abdominal wall endometriosis, extrapelvic endometriosis, scar endometriosis, incisional endometriosis, inguinal endometriosis, umbilical endometriosis, ectopic endometriosis, and cutaneous endometriosis. Articles that included 5 or more cases were included in the review. 29 articles, which included clinical data on 445 patients, met the inclusion criteria. All studies were retrospective cohorts and most (79%) were single-center studies, with only 1 report including more than 2 centers.	The search included all articles from 1951 until August 2006. A single author (JH) extracted data from each article in a standardized manner. If available, the author recorded	the average age at presentation, percentage with symptoms associated with a cesarean section scar, percentage with symptoms associated with a hysterectomy scar, years between the initial surgery and the onset of symptoms, percentage of patients with a concurrent diagnosis of pelvic endometriosis, percentage of patients who presented with pain (other symptoms may have been present in addition to pain), percentage of patients who presented with a mass or swelling (other symptoms may have been present in addition to mass or swelling), percentage of patients who presented with cyclic symptoms related to	abdominal wall endometriosis is a relatively common condition that primarily affects women between 20 and 40 years of age and usually occurs 2 to 5 years after a cesarean section. Patients typically present with a painful mass that may become more symptomatic around her menses. A significant proportion of patients will have an AWE that is not associated with a previous surgical incision.		

				menses (other symptoms may have been present in addition to cyclic symptoms), percentage of patients who had symptoms totally unrelated to a surgical scar, the mean and SD of the size of the endometrioma (largest single dimension), percentage of patients who had a recurrence after resection, and the length of follow-up evaluation.			
(Zhu*, et al.*, 2017)	A retrospective study in Gynaecological department of a teaching hospital in China	abdominal wall endometriosis.	Among the 51 patients, 23 patients were treated with ultrasound-guided HIFU and 28 patients with surgery.	Pain relief and the size change of the nodule after each management were evaluated 1, 3, 6 and 12 months after treatment, respectively. The hospital stay and blood loss were also compared.	No statistically significant differences were observed between the two groups in the pain relief in 1, 3, 6 and 12 months after treatment, respectively. The hospital stay was clearly shorter in the HIFU group than in the surgery group. Change in nodules was more remarkable in the group treated with surgery; no palpable nodules existed in most patients in the surgery group. HIFU had more advantages over surgery, such as no blood loss, no new scar, no anaesthesia and lower pain score immediately after treatment.	Based on our results, it appears that either HIFU or surgery is safe and effective in treating patients with AWE in short-term. Compared with surgery, HIFU treatment for AWE has the advantages of shorter hospital stay, no blood loss, no new scar, no anaesthesia and a lower immediate pain score.	ultrasound-guided HIFU OR surgery for AWE

INCLUDED AS BACKGROUND INFORMATION
(Keckstein*, et al.*, 2020, Veeraswamy*, et al.*, 2010)

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	There are no studies comparing medical and surgical treatment for abdominal extrapelvic endometriosis. Data are mainly available from retrospective (case) reports and show feasibility of surgery and effectiveness towards symptoms relief. A few studies have a also reported on recurrence rates. Evidence for medical treatment is even more scarce, but based on indirect evidence of pelvic endometriosis, benefit can be expected Quality of evidence: ⊕◯◯◯

Balance between desirable and undesirable outcomes	Symptom relief versus complications, side effects, recurrence
Balance between different outcomes	There are too few data to make any strong recommendations on one treatment over another. In general, surgical treatment seems the most applied.
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	Not relevant as different treatments are presented as an option
RECOMMENDATION	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.

Thoracic endometriosis

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Andres, *et al.*, 2020)	Systematic review of 179 articles, mostly case reports and series	Thoracic endometriosis Diaphragmatic and Pleural Endometriosis Lung endometriosis	Surgical/medical treatment	Feasibility complications	**pleural and diaphragm endometriosis** The surgical approach of choice for the treatment of diaphragm and pleural endometriosis was video-assisted thoracoscopic surgery (VATS) in 12 of 13 studies (72%, 443/ 615). The main surgical VATS finding was a diaphragmatic defect, often with visualization of the liver through the defect. 3 studies reported the need for a thoracotomy for patients who have had a previous thoracotomy or with complex lesions Surgical treatment of diaphragmatic lesions, reported in 370 patients, included coagulation of superficial endometriotic implants (27.2%; 101/370), and partial diaphragm resection and suturing (78.1%; 289/370) for deep lesions. Adjuvant hormonal therapy : in 15.5%(77/370) Recurrence of pneumothorax in 29.0% (139/478) of cases of pleural and diaphragm endometriosis. **Lung Endometriosis** Surgical treatment was performed in 82.1%(23/28) cases Most common surgical procedure: VATS (59.0%; 13/22) In 3 cases (10.7%; 3/28) only hormonal treatment with GnRHa. There were no recurrences after surgical or medical treatment (9 studies / 31 patients)		*Data on other extrapelvic endometriosis subtypes/diagnosis /treatment are included in the respective evidence tables*
(Vigueras Smith, *et al.*, 2020)	Review	diaphragmatic endometriosis MEDLINE search	minimally invasive surgical (MIS) treatment		MIS techniques seems to be safe, effective and feasible in tertiary advanced endometriosis centre, offering definitive advantages in terms of hospital stay, post-operative pain and return to normal activity by using several surgical techniques as hydrodissection plus resection, laser CO(2) vaporisation, electrical fulguration, Sugarbaker peritonectomy, partial (shaving) and full-thickness diaphragmatic resection. Symptoms control range from 85% to 100%, with less than 3% of conversion, peri-operative complications and recurrence rate. All cases must be performed by multidisciplinary teams including at least a gynaecologist, thoracic surgeon and anaesthetist.	The lack of prospective evaluation of DE interferes with the understanding about the natural history of disease and treatment results. Therefore, the development of adequate evidence-based recommendations about diagnosis, management and follow-up is difficult at this moment.	
(Joseph and Sahn, 1996)	Review	A MEDLINE search All information given as individual case reports and small series were utilized for this study.	74 of the 110 patients (67%) with thoracic endometriosis had undergone thoracotomy or thoracoscopic examinations as a part of	recurrence rate for pneumothorax at 6 months and 12 months	Compared with hormonal treatment, surgical pleurodesis resulted in low recurrence rate for pneumothorax at 6 months (P = 0.002) and 12 months (P = 0.03) of follow-up. There was no significant difference in recurrence rate for pneumothorax or hemothorax among patients treated with danazol or oral contraceptives.	There is a significant association between the presence of pelvic endometriosis and TES, with the latter occurring approximately 5 years later. Pneumothorax is the most	

		Clinical presentation (see VII.1)	the diagnostic testing or treatment. Combination of hormonal and surgical treatment.			common manifestation. The most plausible explanation for pathogenesis involves peritoneal-pleural movement of endometrial tissue through diaphragmatic defects and microembolization through pelvic veins. Diagnosis is established on clinical grounds in most cases. Surgical pleural abrasion is superior to hormonal treatment in the long-term management of pneumothorax. Earlier diagnosis and effective therapy of TES can decrease the morbidity of this disease in women during their reproductive period.	
(Gil and Tulandi, 2019)	SR	The following medical subject heading terms, keywords, and their combinations were used: "catamenial pneumothorax; thoracic endometriosis; pulmonary endometriosis; and pleural endometriosis." The search was limited to trials in humans and published in English language in the past 20 years up to November 2018. The inclusion criteria were as follows: clinical articles, case series with over 5 patients, cohort studies, reviews, and meta-analyses. The search produced an initial 404 results. Excluded : case studies and videos. 18 studies, with a total of 490 patients, met the inclusion criteria and were selected. Most of the publications were retrospective cohort studies, and 1 study was a prospective study.	surgery and medical treatment presented		History should always include catamenial extrapelvic symptoms such as chest pains, dyspnea, or hemoptysis. Multidisciplinary management including a gynecologist and a thoracic surgeon or pneumologist is beneficial. Because of the rareness of this condition, current evidence is inadequate.	To achieve a better understanding and treatment of this condition, we propose creating a registry on thoracic endometriosis involving gynecologists,pneumologists, and thoracic surgeons.	
(Ceccaroni, *et al.*, 2013)	cohort	7-year single-institution retrospective review. 46 cases with intraoperative diagnosis of diaphragmatic endometriosis were identified.		Median hospital stay was 7 (range 2–21) days. All 14 patients with symptoms suggestive for diaphragmatic endometriosis reported complete pain relief at 30th and 120th postoperative day	Operative findings showed multiple diaphragmatic lesions in 32 (69.5 %) patients and single lesions in 14 (30.4 %). Diaphragmatic implants were distributed on the right side in 40 (86.9 %) patients; in 5 patients (10.8 %) they were bilateral and 1 patient had a single lesion on the left hemidiaphragm. Most of the symptomatic patients were treated by complete excision of the nodules, whereas only three patients referring right upper-quadrant abdominal pain and right shoulder catamenial pain had superficial diaphragmatic endometriosis and were treated by diathermocoagulation.	In our experience, treatment of diaphragmatic endometriosis has been shown to be feasible, cost-effective, and with a low complication rate, thus it can always be justified. However, this kind of surgery should be managed in a referral center by an expert laparoscopic gynecologist with knowledge	Diaphragmatic Treatment

				follow-up examinations.		of oncological surgical techniques, and with the support of a laparoscopic general surgeon and a trained anaesthesiologist.	
(Nezhat, *et al.*, 2014)	cohort	Retrospective, institutional review board–approved case series of 25 consecutive women who underwent combined video-assisted thoracoscopic surgery and traditional laparoscopy for the treatment of abdominopelvic, diaphragmatic, and thoracic endometriosis.	Combination of video-assisted thoracoscopic surgery and traditional laparoscopy for the treatment of abdominopelvic and thoracic endometriosis.	The clinical follow-up period ranged between 3 and 18 months. Overall, all 25 patients noted significant improvement or resolution of their chest complaints. However, before 6 months, many noted occasional chest complaints or pain from the thoracostomy site. In two cases the chest complaints returned, one at 9 months and the other at 12 months.		Because most patients have both pelvic and thoracic symptoms—as was found in 100% of the patients in this series—it is important to assess and treat all areas of disease. A multidisciplinary approach of combined VATS and traditional laparoscopy optimally addresses pelvic, diaphragmatic, and thoracic endometriosis in a single operation. This case series is the largest such case series, to our knowledge, and illustrates the complexity of the disease and the benefit of a multidisciplinary approach.	combined video-assisted thoracoscopic surgery and traditional laparoscopy for the treatment of abdominopelvic, diaphragmatic, and thoracic endometriosis.
(Ciriaco, *et al.*, 2020)	Review (PubMed and Scopus)	Thoracic endometriosis syndrome (TES) 25 studies - 732 patients	analyze the different approaches to generate an ideal diagnosis-treatment algorithm	Information on preoperative exams, surgical technique, postoperative management, and recurrence of disease	Almost all of the patients underwent radiologic pelvis investigation (96%; confidence interval [CI] 87-100). Videothoracoscopy was the preferred surgical technique (84%; 95% CI 66-96). Intraoperative evaluation revealed the presence of diaphragmatic anomalies in 84% of cases (95% CI 73-93). The overall pooled prevalence of concomitant or staged laparoscopy was 52% (95% CI 18-85). Postoperative hormone therapy was heterogeneous with a pooled prevalence of 61% (95% CI 33-86; I(2)=95.6%; p<0.01). Recurrence of symptoms was documented in 27% of patients (95% CI 20-34; I(2)=54.7%; p<0.01).	TES should be managed jointly by thoracic surgeons and gynecologists. Chest-abdomen magnetic resonance imaging seems to offer the most details for TES. Combined or staged videothoracoscopy and laparoscopy can provide adequate information to fine-tune proper surgical treatment and postoperative medical therapy.	The diagnostic-curative path is defined by both thoracic surgeons and gynecologists, consistent with the manifestation of the disease.

INCLUDED AS BACKGROUND INFORMATION
(Keckstein, *et al.*, 2020, Rousset, *et al.*, 2014)

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	There are no studies comparing medical and surgical treatment for thoracic endometriosis. Data are mainly available from retrospective (case) reports and show feasibility of surgery and effectiveness towards symptoms relief. A few studies have a also reported on recurrence rates. Evidence for medical treatment is even more scarce, but based on indirect evidence of pelvic endometriosis, benefit can be expected Quality of evidence: ⊕◯◯◯
Balance between desirable and undesirable outcomes	Symptom relief versus complications, side effects, recurrence

Balance between different outcomes	There are too few data to make any strong recommendations on one treatment over another. In general, surgical treatment seems the most applied but such surgery required specific skills and expertise and hence should only be performed in a multidisciplinary manner involving a thoracic surgeon and/or other relevant specialists. Medical treatment is considered the safer option
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	Surgery for thoracic endometriosis is feasible, but should be performed in a multidisciplinary manner involving a thoracic surgeon and/or other relevant specialists.
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.

QUESTION VIII.1 IS TREATMENT BENEFICIAL FOR INCIDENTAL FINDING OF ASYMPTOMATIC ENDOMETRIOSIS?

Surgical treatment

Summary of Findings Table

Not applicable

EVIDENCE TABLE

There are no studies reporting on any surgical or medical interventions for asymptomatic endometriosis.

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Moen and Stokstad, 2002)	CS	39 patients with minimal/mild and 157 controls at tubal ligation. A second look LSK was performed to assess the progression	Second look LSK		Pelvic pain was more frequently reported by controls than by women with endometriosis (28% vs. 6%). There was no significant difference between the groups concerning dysmenorrhea, premenstrual pain, or dyspareunia, nor was there any significant difference in the hysterectomy rate.	According to the data from this study there is little risk that asymptomatic, minimal endometriosis found incidentally will become symptomatic.	

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	No direct evidence (surgery versus expectant management or monitoring). There is very low quality indirect evidence supporting a conclusion that asymptomatic endometriosis is probably not progressive. Evidence (indirect from symptomatic endometriosis) is available on the risks of treatment (observational data only) Quality of evidence: ⊕○○○
Balance between desirable and undesirable outcomes	benefit of surgery: possible prevention of complications (cancer, kidney, bowel) risks of surgery : surgical risks (by definition) + possible negative effect on ovarian reserve
Balance between different outcomes	With low incidence of cancer and/or other complications, the benefits of surgery seem not to outweigh the risks of surgery in women without symptoms (pain/infertility).
Patient values and preference	unclear
Resource use, equity, acceptability and feasibility	Surgery is feasible but with associated costs. Acceptability is questionable
RECOMMENDATION	**Clinicians should not routinely perform surgical excision/ablation for an incidental finding of asymptomatic endometriosis at the time of surgery.**
GPP	**The GDG recommends that clinicians should inform and counsel women about any incidental finding of endometriosis.**

Medical treatment

Summary of Findings Table

Not applicable

EVIDENCE TABLE

There are no studies reporting on any medical interventions for asymptomatic endometriosis.

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	No direct evidence (medical treatment versus expectant management or monitoring) There is very low quality indirect evidence supporting a conclusion that asymptomatic endometriosis is probably not progressive. There is no evidence that medical treatment has a negative effect of disease progression Evidence (indirect from symptomatic endometriosis) is available on the risks of treatment (observational data only) Quality of evidence: ⊕◯◯◯
Balance between desirable and undesirable outcomes	Benefit : possible prevention of complications (cancer, kidney, bowel) – possible prevention of endometriosis becoming worse Risks : limited side effects of medical treatments (OCP), more side effects and possible harms from GnRHa
Balance between different outcomes	With minor risks, possible benefits may outweigh the risks. Furthermore, OCP may be indicated for contraception anyway.
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	Resource use is limited
RECOMMENDATION	Clinicians should not prescribe medical treatment in women with incidental finding of endometriosis.

QUESTION VIII.2 IS LONG TERM MONITORING OF WOMEN WITH ASYMPTOMATIC ENDOMETRIOSIS BENEFICIAL IN PREVENTING ADVERSE OUTCOMES?

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Alcazar*, et al.*, 2005)	CS	120 asymptomatic patients with endometrioma	Long term TVS follow-up		With a median follow-up of 42 months (range: 18-94 months), most lesions remained unchanged, both in size and sonographic appearance. Ten cysts (8.3%) disappeared during follow-up, all of them after more than 2 years of follow-up. No patient has developed signs or symptoms suggesting ovarian cancer.		
(Maouris, 1991)	SR	Review of studies of asymptomatic minimal-mild endometriosis treated by expectant management in case of infertile women. No of patients: 17 and 20 in the mentioned studies	In this studies second look laparoscopy was performed in a small number of women with endometriosis received placebo. The second look laparoscopy was performed 6 months later.		The first mentioned study: 17 patients:6 months after the first laparoscopy the severity of endometriosis was found unchanged in 4 cases, improved in 5, became worse in 8 patients. In the second study: out of 20 patients, 3 became pregnant, 10 were unchanged, 3 improved, 4 became worse after 6 months.	In asymptomatic infertile women with minimal or mild endometriosis, expectant management followed by second laparoscopy and selective treatment could form the basis for valuable research. Expectant management with or without second laparoscopy would be a benefit to patients by avoiding unnecessary treatment and allow early conception in a significant proportion.	
(Pearce*, et al.*, 2012).	SR	13 ovarian cancer case-control studies; 13 226 controls and 7911 women with invasive ovarian cancer			Self-reported endometriosis was associated with a significantly increased risk of clear-cell (136 [20·2%] of 674 cases vs 818 [6·2%] of 13 226 controls, odds ratio 3·05, 95% CI 2·43-3·84, p<0·0001), low-grade serous (31 [9·2%] of 336 cases, 2·11, 1·39-3·20, p<0·0001), and endometrioid invasive ovarian cancers (169 [13·9%] of 1220 cases, 2·04, 1·67-2·48, p<0·0001). No association was noted between endometriosis and risk of mucinous (31 [6·0%] of 516 cases, 1·02, 0·69-1·50, p=0·93) or high-grade serous invasive ovarian cancer (261 [7·1%] of 3659 cases, 1·13, 0·97-1·32, p=0·13), or borderline tumours of either subtype (serous 103 [9·0%] of 1140 cases, 1·20, 0·95-1·52, p=0·12, and mucinous 65 [8·5%] of 767 cases, 1·12, 0·84-1·48, p=0·45).	increased risk of specific subtypes of ovarian cancer in women with endometriosis.	
(Serati*, et al.*, 2013)	cohort	A total of 25 asymptomatic patients: 12 patients with DE (group 1) and 13 patients with ovarian	Prospective urodynamic study to assess bladder function in asymptomatic DIE/ovarian endometriosis patients		urodynamic diagnosis of detrusor overactivity was correlated with the presence of deep infiltrating Endometriosis (group 1, 91.7% [11/12] vs. group 2, 7.7% [1/13]). All involuntary detrusor contractions were detected only during the filling phase. All cystometry parameters were found to be altered in group 1 and statistically different between the two groups. No pressure/ flow	DE could significantly impair detrusor functions. A preoperative urodynamic evaluation allows the attainment of important	Well designed study with relevant outcome. Small

		endometriosis (group 2, control group).			study parameter Significantly differed between the two groups, besides maximal detrusor pressure (46 cmH2O [33–79] vs. 29 cmH2O [15–40]), which was significantly higher in group 1. Therefore, all detrusor-related parameters are statistically different between the two groups. Postvoid residual does not reach a statistically significant difference.	functional information, even in asymptomatic patients.	group of patients, not an ideal control group

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	There are no solid data on the benefit of monitoring of asymptomatic endometriosis There is very low quality indirect evidence supporting a conclusion that asymptomatic endometriosis is probably not progressive. Quality of evidence: ⊕◯◯◯
Balance between desirable and undesirable outcomes	Benefit : early detection of complications of endometriosis (kidney, bowel) or other issues (cancer) Risks of monitoring: minor
Balance between different outcomes	As incidental finding of endometriosis is often in older women (presenting for Hx/tubal ligation), "ovarian reserve" is a less important outcome. With low incidence of torsion, rupture, kidney and bowel complications, and low incidence of cancer, monitoring and early detection does not seem to weigh up against burden and costs of monitoring in general, but can be considered. There is no information as to how often and how long the monitoring should continue.. Alternatively, patients with asymptomatic endometriosis can be advised to seek medical help in case of occurrence of any endometriosis-related symptoms.
Patient values and preference	Unclear
Resource use, equity, acceptability and feasibility	Extended monitoring seems feasible but with associated costs
RECOMMENDATION	**Routine ultrasound monitoring of asymptomatic endometriosis can be considered.**

QUESTION IX.1 IS THERE A ROLE FOR PRIMARY PREVENTION OF ENDOMETRIOSIS?

Lifestyle (diet, alcohol, physical activity, smoking)

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion
DIET						
(Parazzini, *et al.*, 2013b)	Systematic review	10 case-control and one cohort study	Association between food intake (nutrients and food groups) and endometriosis. Information on diet was collected using food frequency questionnaires in seven studies, while in one study the questionnaire focused on caffeine and alcohol intake		Women with endometriosis seem to consume fewer vegetables and omega-3 polyunsaturated fatty acids and more red meat, coffee and trans fats but these findings could not be consistently replicated.	At present, evidence supporting a significant association between diet and endometriosis is equivocal. Further studies are needed to clarify the role of diet on endometriosis risk and progression.
(Nodler, *et al.*, 2019)	Prospective cohort study	Among women who completed the questionnaire about their high school diet in 1998, 581 cases of laparoscopically confirmed endometriosis were diagnosed among 32,868 premenopausal women from 1998 to 2013.	This was a prospective cohort study, the Nurses' Health Study II, which has prospectively collected data since 1989. In 1998, when participants were aged 34-51 years, they completed a 124 item food frequency questionnaire about their high school diet.	Cases were defined as those who self-reported laparoscopically confirmed endometriosis. Cox proportional hazard models were used to calculate hazard ratios and 95% confidence intervals for the association between dairy foods and laparoscopically confirmed endometriosis.	Women who consumed more than 4 servings per day of dairy foods during adolescence had a 32% lower risk of laparoscopically confirmed endometriosis during adulthood (95% confidence interval, 0.47-0.96; Ptrend = .04) compared with women consuming 1 or fewer servings per day. The association was similar for low-fat and high-fat dairy foods. Yogurt and ice cream consumption, specifically, were associated with a lower risk of endometriosis. Those who consumed 2 or more servings of yogurt per week as an adolescent had a 29% lower risk of endometriosis diagnosis (95% confidence interval, 0.52-0.97; Ptrend = .02) compared with those consuming less than 1 serving per week. In addition, women who consumed 1 or more servings per day of ice cream per day during adolescence had a 38% lower risk of endometriosis diagnosis (95% confidence interval, 0.40-0.94; Ptrend = .20) compared with those consuming less than 1 serving per week	Dairy consumption, specifically yogurt and ice cream intake, in adolescence may reduce the risk of subsequent endometriosis diagnosis.
(Harris, *et al.*, 2018)	Prospective cohort study	70 835 premenopausal women from 1991 to 2013 as part of the Nurses' Health Study II cohort	Cases were restricted to laparoscopically confirmed endometriosis. Cox proportional hazards models were used to calculate rate ratios (RR) and 95% CI.	Diet was assessed with a validated food frequency questionnaire (FFQ) every 4 years.	During 840 012 person-years of follow-up, 2609 incident cases of laparoscopically confirmed endometriosis were reported (incidence rate = 311 per 100 000 person-years). Authors observed a non-linear inverse association between higher fruit	Higher intake of fruits, particularly citrus fruits, is associated with a lower risk of endometriosis

					consumption and risk of laparoscopically confirmed endometriosis (Psignificance of the curve = 0.005). This inverse association was particularly evident for citrus fruits. Women consuming ≥1 servings of citrus fruits/day had a 22% lower endometriosis risk (95% CI = 0.69-0.89; Ptrend = 0.004) compared to those consuming <1 serving/week. No association was observed between total vegetable intake and endometriosis risk. However, women consuming ≥1 servings/day cruciferous vegetables had a 13% higher risk of endometriosis (95% CI = 0.95-1.34; Ptrend = 0.03) compared to those consuming <1 serving/week. Of the nutrients examined, only beta-cryptoxanthin intake was significantly associated with lower endometriosis risk (RR fifth quintile = 0.88; 95% CI = 0.78-1.00; Ptrend = 0.02).	
(Parazzini, *et al.*, 2013a)	Systematic review and meta-analysis	15 studies		Pooled estimates of the relative risks (RRs) and the corresponding 95% confidence intervals (CIs) were calculated using fixed or, when significant heterogeneity among estimates emerged, random effects models.	The summary estimate was 1.24 (95% CI, 1.12-1.36) for any alcohol intake vs no alcohol intake. Considering the results of the analyses of infrequent, moderate/regular, and heavy alcohol intake vs no alcohol intake, the summary RR estimates were, respectively, 1.14 (95% CI, 0.86-1.52), 1.23 (95% CI, 1.08-1.40), and 1.19 (95% CI, 0.99-1.43). Three studies reported separate results for current and former drinkers, and the summary RR were 1.42 (95% CI, 1.14-1.76) and 1.09 (95% CI, 0.83-1.43), respectively.	The present meta-analysis provides evidence for an association between alcohol consumption and endometriosis risk.
(Qiu, *et al.*, 2020)	Systematic review and meta-analysis	Nine studies were included in this meta-analysis			The pooled results indicated that women with endometriosis had lower vitamin D status than that in controls (SMD - 0.97 ng/mL, 95% CI - 1.80 to - 0.14; p = 0.02), and vitamin D status had a negative correlation with the severity of the disease (stage III-IV vs stage I-II: SMD - 1.33 ng/mL, 95% CI - 2.54 to - 0.12; p = 0.03)	Women with endometriosis had lower vitamin D status when compared with controls, and a negative relationship between vitamin D levels and severity of endometriosis was observed. In addition, hypovitaminosis D was a potential risk factor for endometriosis.
(Hansen and Knudsen, 2013)	Meta-analysis	1433 papers reviewed - 23 articles used, used cocraine analysis techniques	inclusion exclusion was sparse, study period variable	variable outcome measures, different pain scoring tools, recall of nutritional intake which may cause bias. Some did not stratisfy for weight and oral contraceptives and analgesia		litrature sugests that increased 3-Fas, fish oils and PUFAs has positive effect on endometriosis and dysmenorhea indicating that there may be modifyable risk factors - further research is needed

SMOKING						
(Bravi*, et al.*, 2014)	Systematic review and meta-analysis	13,129 women diagnosed with endometriosis, from 38 studies	1. Cases (endometriosis) non-smoker 2. Total non-smokers 3. Cases (endometriosis) smokers 4. Total smokers	Risk of endometriosis in tobacco smokers	As compared to never-smokers, the summary RR were 0.96 (95% CI 0.86 to 1.08) for ever smokers, 0.95 (95% CI 0.81 to 1.11) for former smokers, 0.92 (95% CI 0.82 to 1.04) for current smokers, 0.87 (95% CI 0.70 to 1.07) for moderate smokers and 0.93 (95% CI 0.69 to 1.26) for heavy smokers.	The present meta-analysis provided no evidence for an association between tobacco smoking and the risk of endometriosis.
PHYSICAL ACTIVITY						
(Ricci*, et al.*, 2016)	Systematic review and meta-analysis	Six case-control and 3 cohort studies included 3355 cases for recent PA and 4600 cases for past PA.	Association between endometriosis and physical activity (PA)		The summary OR for endometriosis according to PA level, calculated by the random-effect model, was 0.85 [95% confidence interval (CI) 0.67-1.07] for any recent versus no PA. As compared to no recent PA, ORs for low and moderate/high PA were 1.00 (95% CI: 0.68-1.28) and 0.75 (95% CI: 0.53-1.07), respectively.	Though it suggests that PA may reduce the risk of endometriosis, this meta-analysis does not conclusively support the hypothesis.

INCLUDED AS BACKGROUND INFORMATION
(Missmer*, et al.*, 2010).

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	Low quality evidence seems to support a link between healthy lifestyle (fruit intake, vitamin D, alcohol consumption). Evidence does not support a link between physical activity or smoking and endometriosis Quality of evidence: ⊕⊕◯◯
Balance between desirable and undesirable outcomes	Benefits: probable beneficial effects of healthy lifestyle/diet, regardless of endometriosis. Risks: none.
Balance between different outcomes	The benefit of a healthy lifestyle/diet outweigh the risks in general and possibly also towards the development of endometriosis.
Patient values and preference	Unclear.
Resource use, equity, acceptability and feasibility	To the best of our knowledge, the proposal of healthy lifestyle/diet could be considered a feasible and acceptable option, without additional direct and/or indirect costs.
RECOMMENDATION	**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.**

Hormonal contraceptive

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Vercellini, *et al.*, 2011)	Systematic review and meta-analysis	608 potentially relevant studies and 18 studies (6 cross-sectional, 7 case-control and 5 cohort) were selected			Pooling of the results derived from all the included reports independently from study design, yielded a common relative risk of 0.63 [95% confidence interval (CI), 0.47-0.85] for current OC users, 1.21 (95% CI, 0.94-1.56) for past users and 1.19 (95% CI, 0.89-1.60) for ever users.	The risk of endometriosis appears reduced during OC use. However, it is not possible to exclude the possibility that the apparent protective effect of OC against endometriosis is the result of postponement of surgical evaluation due to temporary suppression of pain symptoms. Confounding by selection and indication biases may explain the trend towards an increase in risk of endometriosis observed after discontinuation, but further clarification is needed. To date, the hypothesis of recommending OCs for primary prevention of endometriosis does not seem sufficiently substantiated.	

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	Low quality evidence from a systematic reviews and meta-analyses of epidemiological/observational studies, concluding that the risk of endometriosis appears reduced during OC use, but this observation can be linked by postponement of surgical evaluation due to temporary suppression of pain symptoms. Quality of evidence: ⊕⊕◯◯
Balance between desirable and undesirable outcomes	Benefits: possible lower risk of endometriosis. Risks: risks associated with the use of OCP
Balance between different outcomes	Recommending OCs for primary prevention of endometriosis does not seem sufficiently substantiated, as it is not possible to exclude the possibility that the apparent protective effect of OC against endometriosis is the result of postponement of surgical evaluation due to temporary suppression of pain symptoms
Patient values and preference	Unclear.
Resource use, equity, acceptability and feasibility	To date, the available low quality evidence does not justify the proposal of using OC for primary prevention of endometriosis.
RECOMMENDATION	**The usefulness of hormonal contraceptives for the primary prevention of endometriosis is uncertain.**

Other factors

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion
(Shafrir, *et al.*, 2018)	Non-systematic review of epidemiological studies				Characteristics robustly associated with a greater risk for endometriosis include early age at menarche, short menstrual cycle length, and lean body size, whereas greater parity has been associated with a lower risk. Relationships with other potential characteristics including physical activity, dietary factors, and lactation have been less consistent, partially because of the need for rigorous data collection and a longitudinal study design.	Critical methodologic complexities include the need for a clear case definition; valid selection of comparison/control groups; and consideration of diagnostic bias and reverse causation when exploring demographic characteristics, medical history, and lifestyle factors.
(Parazzini, *et al.*, 2017)	Non-systematic review	Not applicable	Not applicable	Not applicable	Not applicable	Social class and family history apart, the factors most consistently associated with endometriosis are early age at menarche and long and heavy menstrual cycles. These menstrual characteristics (together with nulliparity) reflect increased exposure to menstruation. The other main risk factors are pigmentary traits and sun habits, alcohol intake, use of oral contraceptives, and environmental factors such as exposure to polychlorinated biphenyls and dioxin. All of these factors support a potential role of hormonal mileau and inflammation in the pathogenesis of endometriosis. There is a clear association between endometriosis and gastrointestinal and immunological diseases, ovarian cancer and other gynaecological cancers, and thyroid cancer.
CHEMICALS						
(Cano-Sancho, *et al.*, 2019)	Systematic review and meta-analysis	Of the 51 studies retained for the full-text screening, 17 provided effect sizes and metrics sufficient for pooling estimates through meta-analysis.	Only human epidemiological studies were considered, independent of participant age, body mass index or life-stage. Studies reporting individual measures of exposure to organochlorine chemicals (OCCs) were included, considering but not limited to polychlorinated	The primary health outcome was presence of endometriosis, including all sub-types.	The overall odds ratios and 95% confidence intervals were 1.65 (1.14; 2.39) for dioxins (n = 10), 1.70 (1.20; 2.39) for PCBs (n = 9), and 1.23 (1.13; 1.36) for OCPs (n = 5). Despite being statistically significant, these estimates should be considered with caution given the notable heterogeneity and small estimated effect size. Misclassification of exposure, due to varying laboratory detection rate capabilities, and disease status, due to varying definitions of endometriosis, were identified as major sources of uncertainty.	

			dibenzodioxins and dibenzofurans (PCDD/Fs), polychlorinated biphenyls (PCBs), or organochlorine pesticides (OCPs).			
NICKEL						
(Yuk, *et al.*, 2015)	Cross-sectional study	4,985 women were selected from the NHIS cohort database and divided into an endometriosis group (997 women) and a control group (3,988 women).	Endometriosis group was selected according to diagnosis code (N80.X), surgery codes, and drug codes during the years 2009~2013. The controls were randomly matched to the endometriosis patients at a ratio of 4:1 by age and socioeconomic status. Patients with nickel allergy were defined in the cohort dataset as those with a simultaneous diagnosis code (L23.0) and patch test code during 2002~2008.		The number of patients with nickel allergy in the endometriosis group was eight (0.8%), and that in the control group was thirteen (0.3%). After adjustment for age and socioeconomic status, the rate of nickel allergy in was higher in the endometriosis group than in the control group [odds ratio: 2.474; 95% confidence interval: 1.023~5.988; p = 0.044].	

EVIDENCE TO RECOMMENDATIONS

No recommendations formulated

Genetic marker

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion
(Sapkota, *et al.*, 2015)	Systematic review of genome-wide and candidate-gene association studies				Genome-wide significant evidence for rs7521902, rs13394619, rs6542095, rs12700667, rs7739264, and rs1537377. Notably, three coding variants in GREB1 (near rs13394619) and CDKN2B-AS1 (near rs1537377) also showed nominally significant associations with endometriosis	
(Sapkota, *et al.*, 2017)	Systematic review and meta-analysis	11 genome-wide association case-control data sets, totalling 17,045 endometriosis cases and 191,596 controls			Five novel loci significantly associated with endometriosis risk (P<5 × 10-8), implicating genes involved in sex steroid hormone pathways (FN1, CCDC170, ESR1, SYNE1 and FSHB). Conditional analysis identified five secondary association signals, including two at the ESR1 locus, resulting in 19 independent single nucleotide polymorphisms (SNPs) robustly associated with endometriosis, which together explain up to 5.19% of variance in endometriosis	These results highlight novel variants in or near specific genes with important roles in sex steroid hormone signalling and function

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	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.
Balance between desirable and undesirable outcomes	Benefits: probable beneficial effects due to the reduction of unnecessary genetic tests and anxiety. Risks: to date, considering that no genetic test could be considered reliable for the diagnosis of endometriosis, we could not identify any risk of no testing.
Balance between different outcomes	Genetic testing for identifying a high-risk population for developing endometriosis, should be limited to a research setting.
Patient values and preference	In case of accurate and appropriate counselling, we can expect an adequate compliance of the patients about the proposal of avoiding genetic tests.
Resource use, equity, acceptability and feasibility	The avoidance of unnecessary genetic tests may lead to significant reduction of costs for the public health system and patients.
RECOMMENDATION	**Genetic testing in women with suspected or confirmed endometriosis should only be performed within a research setting.**

QUESTION X.1.A ARE ENDOMETRIOSIS PATIENTS AT INCREASED RISK OF CANCER?

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Kvaskoff, *et al.*, 2020)	meta-analysis of studies investigating the association between endometriosis and cancer risk PubMed and Embase databases for eligible studies from inception through 24 October 2019.	49 population-based case-control and cohort studies (cross-sectional studies and case reports were excluded) 26 studies were scored as having a 'serious'/'critical' risk of bias, and the remaining 23 'low'/'moderate'.	/	summary relative risks (SRR)	Cancer-specific analyses showed a positive association between endometriosis and ovarian cancer risk (SRR=1.93, 95% CI=1.68-2.22; n=24 studies) that was strongest for clear cell (SRR=3.44, 95% CI=2.82-4.42; n=5 studies) and endometrioid (SRR=2.33, 95% CI=1.82-2.98; n=5 studies) histotypes (Pheterogeneity < 0.0001), although with significant evidence of both heterogeneity across studies and publication bias (Egger's and Begg's P-values<0.01). A robust association was observed between endometriosis and thyroid cancer (SRR=1.39, 95% CI =1.24-1.57; n=5 studies), a very small association with breast cancer (SRR=1.04, 95% CI =1.00-1.09; n=20 studies) and no association with colorectal cancer (SRR=1.00, 95% CI =0.87-1.16; n=5 studies). The association with endometrial cancer was not statistically significant (SRR=1.23, 95% CI =0.97-1.57; n=17 studies) overall and wholly null when restricted to prospective cohort studies (SRR=0.99, 95% CI =0.72-1.37; n=5 studies). The association with cutaneous melanoma was also non-significant (SRR=1.17, 95% CI =0.97-1.41; n=7 studies) but increased in magnitude and was statistically significant when restricted to studies with low/moderate risk of bias (SRR=1.71, 95% CI=1.24-2.36, n=2 studies). The most robust finding both in terms of statistical significance and magnitude of effect was an inverse association with cervical cancer (SRR=0.68, 95% CI =0.56-0.82; n=4 studies); however, this result has a high potential to reflect heightened access to detection of dysplasia for women who reached an endometriosis diagnosis and is thus likely not causal. Several additional cancer types were explored based on <4 studies.	Endometriosis was associated with a higher risk of ovarian and thyroid, and minimally (only 4% greater risk) with breast cancer, and with a lower risk of cervical cancer.	

INCLUDED AS BACKGROUND INFORMATION *These studies are included in the review Kvaskoff 2020, and some details are highlighted in the text*
(Farland, *et al.*, 2016, Kobayashi, *et al.*, 2007, Mogensen, *et al.*, 2016, Moseson, *et al.*, 1993, Saavalainen, *et al.*, 2018, Weiss, *et al.*, 1999).

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	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%). (Systematic review and meta-analysis, based on observational data) Quality of evidence: ⊕⊕◯◯
Balance between desirable and undesirable outcomes	NA
Balance between different outcomes	NA
Patient values and preference	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.
Resource use, equity, acceptability and feasibility	NA
RECOMMENDATION	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.
GPP	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).

QUESTION X.1B WHAT INFORMATION COULD CLINICIANS PROVIDE TO WOMEN WITH ENDOMETRIOSIS REGARDING THEIR RISK OF DEVELOPING CANCER?

NARRATIVE QUESTION

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Not applicable

INCLUDED REFERENCES (Narrative question)
none

EVIDENCE TO RECOMMENDATIONS

Not applicable

QUESTION X.1C ARE SOMATIC MUTATIONS IN DEEP ENDOMETRIOSIS OF PATIENTS WITHOUT CANCER PREDICTIVE FOR OVARIAN CANCER DEVELOPMENT AND/OR PROGRESSION?

NARRATIVE QUESTION

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Not applicable

INCLUDED REFERENCES (Narrative question)
(Anglesio and Yong, 2017) (Guo, 2020) (Vigano, *et al.*, 2006) (Kvaskoff, *et al.*, 2020) (Van Gorp, *et al.*, 2004) (Akahane, *et al.*, 2007) (Amemiya, *et al.*, 2004) (Borrelli, *et al.*, 2016) (Er, *et al.*, 2016) (Siufi Neto, *et al.*, 2014) (Bulun, *et al.*, 2019) (Yong, *et al.*, 2021) (Suda, *et al.*, 2018) (Anglesio, *et al.*, 2015) (Anglesio, *et al.*, 2017) (Lac, *et al.*, 2019b) (Lac, *et al.*, 2019a)

EVIDENCE TO RECOMMENDATIONS

Not applicable

The GDG formulated the following 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

QUESTION X.1D DOES THE USE OF HORMONE TREATMENTS INCREASE THE RISK OF CANCER?

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Berlanda, *et al.*, 2016)	Narrative review			Formulations of estro-progestins that contain less than 50 µg of estrogen are associated with a low risk of venous thrombosis, myocardial infarction and stroke. When considering the neoplastic effects, data suggest that the overall risk of invasive cancer by age 60 is not increased in previous users of hormonal contraceptives. The use of progestins for contraception has never been associated with an increased risk of breast cancer, venous throm- boembolism or bone fractures. Although more data on long-term therapy with progestins are needed, treatment of endometriosis with progestins may be feasible in women with metabolic or cardiovascular contraindications to estroprogestin. The other medications for the treatment of pain associated with endometriosis are less appropriate for long term administration because of side effects (danazol and GnRH analogues), costs (aromatase inhibitors and GnRH agonists) or necessity of complex regimens of associations (GnRH ago- nists and add back therapy or aromatase inhibitors plus progestins).		
(Butt, *et al.*, 2018)	A nationwide prospective cohort study	pre-menopausal women (all women in Denmark in the age range of 15-49 years without previous cancer or venous thrombosis from 1995 to 2014.) All models were adjusted for age, completed or ongoing education, polycystic ovary syndrome, endometriosis and among parous women; parity, age at first birth, smoking and body mass index.	hormonal contraception	risk of developing pancreatic cancer	Among 1.9 million women who were followed on average for 11.4 years, 235 pancreatic cancers occurred. Compared to never users, ever users of any type of hormonal contraception had a relative risk (RR) of pancreatic cancer of 0.90 (95% CI 0.68-1.19). No overall association between duration of hormonal contraceptive use and pancreatic cancer risk was found. Neither was long-term use of hormonal contraception associated with pancreas cancer, RR: 0.83 (95% CI 0.47-1.50). The risk did not vary between users of combined and progestogen-only products.	Compared to never users the risk of pancreatic cancer is not significantly higher among current and recent users of contemporary hormonal contraception	
(Braganza, *et al.*, 2014)	cohort study	data from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, which enrolled 70,047 women, 50 to 78 years old follow-up :median, 11 years	associations of self-reported history of benign breast and gynecologic conditions, reproductive factors, and exogenous sex hormone use	thyroid cancer risk	Older age at natural menopause (≥55 vs. <50 years; HR, 2.24; 95% CI, 1.20-4.18), greater estimated lifetime number of ovulatory cycles (≥490 vs. <415 cycles; HR, 2.40; 95% CI, 1.33-4.30), greater number of live births (≥5 vs. 1-2; HR, 1.72; 95% CI, 1.05-2.82), and history of uterine fibroids (HR, 1.72; 95% CI, 1.18-2.50) were associated with an increased risk of thyroid cancer.	In general, we found that factors reflecting a greater length of exposure to endogenous hormones, particularly during the reproductive years, were associated with risk of postmenopausal thyroid cancer.	

		127 women were diagnosed with first primary thyroid cancer.			Earlier age at menarche, greater number of reproductive years, history of a tubal ligation, and history of ovarian cysts were nonsignificantly associated with increased thyroid cancer risk. No associations were observed for OCP use, menopausal hormone therapy, or history of benign breast disease or endometriosis.		
(Zucchetto, *et al.*, 2009)	case-control study in Italy	454 women with endometrial cancer and 908 hospital controls.	menstrual and reproductive variables, breastfeeding, exogenous hormones, and gynecological conditions	endometrial cancer risk	Endometrial cancer risk was inversely associated with age at menarche (OR = 0.7, 95% CI = 0.5-1.0, for > or =14 vs. <12 years), and directly associated with age at menopause (OR = 1.8, 95% CI = 1.1-2.7, for > or =55 vs. <50 years) and years of menstruation (OR = 2.4, 95% CI = 1.7-3.4, for highest vs. lowest tertile). Multiparity strongly reduced the risk among women under 60 years of age (OR = 0.3, 95% CI = 0.2-0.6, for > or =3 deliveries vs. <2). OCP use conferred a 40% reduced risk (95% CI = 0.4-1.0), irrespective of time since cessation. Although based on small numbers, **women with a history of treated infertility (OR = 2.7, 95% CI = 1.1-6.4) or endometriosis (OR = 4.0, 95% CI = 1.0-15.5) were at increased risks.** No significant associations with endometrial cancer risk emerged for age at first/last birth, breastfeeding, menopausal status, hormone replacement therapy, and history of uterine fibromyomas or polycystic ovary.	This study confirms the importance of multiparity, years of menstruation, and oral contraceptive use in endometrial cancer etiology, thus contributing to identify women at elevated risk of such neoplasm.	
(Havrilesky, *et al.*, 2013)	meta-analysis (PubMed, Embase, the Cochrane Database of Systematic Reviews, and ClinicalTrials.gov for studies published from January 1990 to June 2012,)	55 studies met inclusion criteria.	oral contraceptive pills (OCPs)	ovarian cancer risk	A random-effects meta-analysis of 24 case-control and cohort studies : - significant reduction in ovarian cancer incidence in ever-users compared with never-users (OR 0.73, 95% CI 0.66-0.81). - a significant duration-response relationship, with reduction in incidence of more than 50% among women using OCPs for 10 or more years. - lifetime reduction in ovarian cancer attributable to the use of OCPs is approximately 0.54% for a number-needed-to-treat of approximately 185 for a use period of 5 years.	Significant duration-dependent reductions in ovarian cancer incidence in the general population are associated with OCP use.	

(Wentzensen, *et al.*, 2016)	Cohort study	Among 1.3 million women from 21 studies, 5,584 invasive epithelial ovarian cancers were identified (3,378 serous, 606 endometrioid, 331 mucinous, 269 clear cell, 1,000 other).	14 hormonal, reproductive, and lifestyle factors by histologic subtype in the Ovarian Cancer Cohort Consortium (OC3).	associations for all invasive cancers by histology - ovarian cancer	Most risk factors exhibited significant heterogeneity by histology. Higher parity was most strongly associated with endometrioid (RR per birth, 0.78; 95% CI, 0.74 to 0.83) and clear cell (RR, 0.68; 95% CI, 0.61 to 0.76) carcinomas (P value for heterogeneity [P-het] < .001). Similarly, age at menopause, endometriosis, and tubal ligation were only associated with endometrioid and clear cell tumors (P-het ≤ .01). Family history of breast cancer (P-het = .008) had modest heterogeneity. Smoking was associated with an increased risk of mucinous (RR per 20 pack-years, 1.26; 95% CI, 1.08 to 1.46) but a decreased risk of clear cell (RR, 0.72; 95% CI, 0.55 to 0.94) tumors (P-het = .004). Unsupervised clustering by risk factors separated endometrioid, clear cell, and low-grade serous carcinomas from high-grade serous and mucinous carcinomas.	The heterogeneous associations of risk factors with ovarian cancer subtypes emphasize the importance of conducting etiologic studies by ovarian cancer subtypes. Most established risk factors were more strongly associated with nonserous carcinomas, which demonstrate challenges for risk prediction of serous cancers, the most fatal subtype.	
(Michels, *et al.*, 2018)	Cohort study	The prospective NIH-AARP Diet and Health Study (enrolled 1995-1996, followed until 2011), with population-based recruitment of AARP members in 6 states and 2 metropolitan areas. All analyses included at least 100000 women who reported OC use at enrollment. We identified 1241 ovarian, 2337 endometrial, 11114 breast, and 3507 colorectal cancer cases during follow-up. adjusted for age, race, age at menarche, and the modifiers of interest. age 50 to 71 years (median, 62 years) at enrollment and largely white (91%) and postmenopausal (96%).	Duration of OC use (never or <1 year [reference], 1-4, 5-9, or >/=10 years).	Development of ovarian, endometrial, breast, and colorectal cancers. We examined effect modification by modifiable lifestyle characteristics: cigarette smoking, alcohol consumption, BMI and physical activity.	For ovarian cancer, OC use-associated risk reductions strengthened with duration of use (long-term OC use [>/=10 years] HR, 0.60; 95% CI, 0.47-0.76; P < .001 for trend) and were similar across modifiable lifestyle factors. Risk reductions for endometrial cancer strengthened with duration of use (long-term OC use HR, 0.66; 95% CI, 0.56-0.78; P < .001 for trend); the most pronounced reductions were among long-term OC users who were smokers (HR, 0.47; 95% CI, 0.25-0.88), had obese BMIs (0.36; 95% CI, 0.25-0.52), and who exercised rarely (HR, 0.40; 95% CI, 0.29-0.56). Associations between OC use and breast and colorectal cancers were predominantly null.	Long-term OC use is consistently associated with reduced ovarian cancer risk across lifestyle factors. We observed the greatest risk reductions for endometrial cancer among women at risk for chronic diseases (ie, smokers, obese BMI). Oral contraceptive use may be beneficial for chemoprevention for a range of women with differing baseline cancer risks.	associations between duration of OC use and risk of specific cancers were modified by lifestyle characteristics.
(Smith, *et al.*, 2003).	Review	28 eligible studies 12531 women with cervical cancer.	Human papillomavirus (HPV) infection OCP use	invasive and in situ cervical cancer	Compared with never users of OCP, the RR of cervical cancer increased with increasing duration of use: for OCP< 5 years, 5-9 years, and >10 years, resp, the summary RR were 1.1 (95% CI 1.1-1.2),	Although long duration use of OCP is associated with an increased risk of cervical cancer, the public health implications of these	

					1.6 (1.4-1.7), and 2.2 (1.9-2.4) for all women; and 0.9 (0.7-1.2), 1.3 (1.0-1.9), and 2.5 (1.6-3.9) for HPV positive women. The results were broadly similar for invasive and in situ cervical cancers, for squamous cell and adenocarcinoma, and in studies that adjusted for HPV status, number of sexual partners, cervical screening, smoking, or use of barrier contraceptives. The limited available data suggest that the relative risk of cervical cancer may decrease after use of oral contraceptives ceases. However, study designs varied and there was some heterogeneity between study results.	findings depend largely on the extent to which the observed associations remain long after use of hormonal contraceptives has ceased, and this cannot be evaluated properly from published data	
(Gierisch, *et al.*, 2013)	systematic review (PubMed, Embase, and Cochrane Database of Systematic Reviews)	We included 44 breast, 12 cervical, 11 colorectal, and 9 endometrial cancers studies.	Oral contraceptive use	risk of breast, cervical, colorectal, and endometrial cancers	Breast cancer incidence was slightly but significantly increased in users (OR, 1.08; CI, 1.00-1.17); results show a higher risk associated with more recent use of oral contraceptives. Risk of cervical cancer was increased with duration of oral contraceptive use in women with human papillomavirus infection; heterogeneity prevented meta-analysis. Colorectal cancer (OR, 0.86; CI, 0.79-0.95) and endometrial cancer incidences (OR, 0.57; CI, 0.43-0.77) were significantly reduced by oral contraceptive use.	Compared with never use, ever use of oral contraceptives is significantly associated with decreases in colorectal and endometrial cancers and increases in breast cancers. Although elevated breast cancer risk was small, relatively high incidence of breast cancers means that oral contraceptives may contribute to a substantial number of cases.	

INCLUDED AS BACKGROUND INFORMATION
(Ferrero, *et al.*, 2015, Ferrero, *et al.*, 2018, Morch, *et al.*, 2018)

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	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. Quality of evidence: ⊕◯◯◯
Balance between desirable and undesirable outcomes	Benefits: relief of symptoms related to endometriosis Harms : possible higher risk of cancer

Balance between different outcomes	Evidence is reassuring towards the risks of cancer, and hence OCP should not be withtheld for that indication
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	NA
RECOMMENDATION	Clinicians should reassure women with endometriosis about the risk of malignancy associated with the use of the oral contraceptive pill (OCP).

QUESTION X.2 SHOULD WOMEN WITH ENDOMETRIOSIS BE MONITORED FOR DETECTION OF MALIGNANCY?

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Kvaskoff, *et al.*, 2020)	meta-analysis of studies investigating the association between endometriosis and cancer risk PubMed and Embase databases for eligible studies from inception through 24 October 2019.	49 population-based case-control and cohort studies (cross-sectional studies and case reports were excluded) 26 studies were scored as having a 'serious'/'critical' risk of bias, and the remaining 23 'low'/'moderate'.	/	summary relative risks (SRR)	Cancer-specific analyses showed a positive association between endometriosis and ovarian cancer risk (SRR=1.93, 95% CI=1.68-2.22; n=24 studies) that was strongest for clear cell (SRR=3.44, 95% CI=2.82-4.42; n=5 studies) and endometrioid (SRR=2.33, 95% CI=1.82-2.98; n=5 studies) histotypes (Pheterogeneity < 0.0001), although with significant evidence of both heterogeneity across studies and publication bias (Egger's and Begg's P-values<0.01). A robust association was observed between endometriosis and thyroid cancer (SRR=1.39, 95% CI =1.24-1.57; n=5 studies), a very small association with breast cancer (SRR=1.04, 95% CI =1.00-1.09; n=20 studies) and no association with colorectal cancer (SRR=1.00, 95% CI =0.87-1.16; n=5 studies). The association with endometrial cancer was not statistically significant (SRR=1.23, 95% CI =0.97-1.57; n=17 studies) overall and wholly null when restricted to prospective cohort studies (SRR=0.99, 95% CI =0.72-1.37; n=5 studies). The association with cutaneous melanoma was also non-significant (SRR=1.17, 95% CI =0.97-1.41; n=7 studies) but increased in magnitude and was statistically significant when restricted to studies with low/moderate risk of bias (SRR=1.71, 95% CI=1.24-2.36, n=2 studies). The most robust finding both in terms of statistical significance and magnitude of effect was an inverse association with cervical cancer (SRR=0.68, 95% CI =0.56-0.82; n=4 studies); however, this result has a high potential to reflect heightened access to detection of dysplasia for women who reached an endometriosis diagnosis and is thus likely not causal. Several additional cancer types were explored based on <4 studies.	Endometriosis was associated with a higher risk of ovarian and thyroid, and minimally (only 4% greater risk) with breast cancer, and with a lower risk of cervical cancer.	

INCLUDED AS BACKGROUND INFORMATION *These studies are included in the review Kvaskoff 2020, and some details are highlighted in the text*
(Berek, *et al.*, 2010, Buys, *et al.*, 2011, Jacobs, *et al.*, 2016, Parker, *et al.*, 2009)

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	Evidence shows a small increase in the lifetime risk of ovarian cancer in endometriosis patients Quality of evidence: ⊕⊕◯◯
Balance between desirable and undesirable outcomes	Benefit of monitoring : early detection/treatment of ovarian cancer Risls : false-positive test results, burden of monitoring

Balance between different outcomes	Given the small increase in the lifetime risk of ovarian cancer in endometriosis patients, regular screening through serum CA-125 measurements or transvaginal ultrasound has no benefit on early detection or mortality reduction for ovarian cancer. Conversely, significant harms have been reported for women receiving false-positive test results. Hence, systematic monitoring for cancer is not recommended in avbsence of additional risk factors
Patient values and preference	NA
Resource use, equity, acceptability and feasibility	Monitoring has significant impact on resources.
RECOMMENDATION	In women with endometriosis, clinicians should not systematically perform cancer screening beyond the existing population-based cancer screening guidelines.
GPP	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.

QUESTION X.3 DOES SURGERY FOR ENDOMETRIOSIS CHANGE THE FUTURE RISK OF CANCER?

Summary of Findings Table

Not applicable

EVIDENCE TABLE

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Melin, *et al.*, 2013)	Nested case-control study	Endometriosis 220 cases and 416 controls All women with a first-time discharge diagnosis of endometriosis in 1969-2007 were identified using the National Swedish Patient Register and constituted our study base.	Hormonal and surgical treatments	risk of epithelial ovarian cancer	There was a significant association between one-sided oophorectomy, as well as for radical extirpation of all visible endometriosis, and ovarian cancer risk in both univariate analyses (crude OR 0.42, 95% CI 0.28-0.62 and OR 0.37, 95% CI 0.25-0.55, respectively) and multivariate analyses (adjusted OR 0.19, 95% CI 0.08-0.46 and OR 0.30, 95% CI 0.12-0.74, respectively).	One-sided oophorectomy as well as radical extirpation of all visible endometriosis is protective against later development of ovarian cancer	
(Rossing, *et al.*, 2008).	case-control study	812 women with ovarian cancer diagnosed in western Washington State from 2002 to 2005 1,313 population-based controls.	in-person interviews - prior diagnosis of, and ovarian surgery following, ovarian cysts and endometriosis	Risk of epithelial ovarian cancer	The risk of a borderline mucinous ovarian tumor associated with a history of an ovarian cyst was increased (OR=1.7, 95% CI: 1.0-2.8), but did not vary notably according to receipt of subsequent ovarian surgery. While risk of invasive epithelial ovarian cancer was slightly increased among women with a cyst who had no subsequent ovarian surgery, it was reduced when a cyst diagnosis was followed by surgery (OR = 0.6, 95% CI: 0.4-0.9). This reduction in risk was most evident for serous invasive tumors. Women with a history of endometriosis had a threefold increased risk of endometrioid and clear cell invasive tumors, with a lesser risk increase among women who underwent subsequent ovarian surgery.	Our results suggest differences in the relation of ovarian cysts and endometriosis with risk of specific subtypes of ovarian cancer as well as the possibility that ovarian surgery in women with these conditions may lower the risk of invasive disease	
(Haraguchi, *et al.*, 2016).	Retrospective cross-sectional study	485 women with endometrioma	excision of endometrioma (performed between 1995 and 2004)	Risk of ovarian cancer (Age, rASRM score, cyst diameter, follow-up periods, endometrioma recurrence, and development of ovarian cancer.)	Recurrence of endometrioma was recorded in 121 patients (24.9% of the entire cohort), and 4 patients (0.8% of the entire cohort) developed ovarian cancer. All ovarian cancers developed from a recurrent endometrioma (3.3% of patients who experienced recurrence). Recurrence of endometrioma was significantly associated with ovarian cancer development.	Ovarian cancers can develop after excision of endometrioma and are more likely to arise from recurrent endometrioma. Special care such as rigorous follow-up should be practiced to manage patients who experience recurrence of endometrioma.	

INCLUDED AS BACKGROUND INFORMATION
(Nezhat*, et al.*, 2008, Vercellini*, et al.*, 2009)

EVIDENCE TO RECOMMENDATIONS

The evidence (and its quality)	One very well-conducted retrospective study only, does not show any risk reduction but shows that the rate of ovarian cancer in a sample of women with excised OMA is very low (0.8%) (Haraguchi, 2016) 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 Quality of evidence: ⊕⊕◯◯
Balance between desirable and undesirable outcomes	Benefit ; cancer risk reduction Risk: morbidity, pain, and ovarian reserve
Balance between different outcomes	The potential benefits of surgery should be weighed against the risks of surgery (morbidity, pain, and ovarian reserve).
Patient values and preference	No data
Resource use, equity, acceptability and feasibility	NA
RECOMMENDATION	**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 (OR 0.29). The potential benefits should be weighed against the risks of surgery (morbidity, pain, and ovarian reserve).**

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